LAB MANAGEMENT CRITERIA
Rocky Mountain Health Plans
Effective January 1, 2015
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Dear Provider,

This document provides detailed descriptions of CareCore National’s basic criteria for laboratory services. These criteria are used for the certification of requests and administration of laboratory benefits for our clients for a range of laboratory tests some of which are represented by one CPT or HCPCS code and others represented by several codes. They have been carefully researched and are continually updated in order to be consistent with the most current evidence-based guidelines and recommendations for laboratory testing from national and international medical societies and evidence-based medicine research centers. In addition, the criteria are supplemented by information published in peer reviewed literature. If you believe that our criteria require modification, please send suggested changes with supporting references to the Laboratory Management Program at the address listed below.

Our health plan clients review the development and application of these criteria. Every CareCore National, LLC health plan client develops a unique list of CPT codes that are part of their utilization management programs. Health Plan medical policy supersedes CareCore National, LLC when there is conflict with the CareCore criteria and the health plan medical policy. If you are unsure of whether or not a specific health plan has made modifications to these basic criteria in their medical policy please contact the plan or access the plan’s website for additional information.

CareCore National works hard to make your clinical review experience a pleasant one. For that reason, we have peer reviewers available to assist you should you have specific questions about a procedure. For your convenience, CareCore National’s Customer Service support is available from 7 a.m. to 7 p.m. Our toll free number is (800) 918-8924.

Shelly Weiner, MD, FACR
Associate Chief Medical Officer
CareCore National, LLC
General Information about This Policy Manual

Description
The CareCore National policy manual contains medical and reimbursement policies that are created and approved by CareCore National’s Laboratory Management Program personnel and policy advisors, internal Medical Advisory Committee, and external Medical Advisory Board. CareCore National’s policies are created using evidence-based medicine including, but not limited to, professional society guidelines, consensus statements, and peer-reviewed literature. CareCore National’s policies are intended to provide a library for adoption or a basis for development of tailored coverage criteria for a Health Plan.

Purpose
To establish evidence-based definitions, decision support, medical necessity criteria, coverage limitations, and payment rules for molecular and genetic testing.

This manual is organized into the following sections:

Molecular and Genetic Clinical Use Policies
The policies in this section are intended to provide general policy guidance for the common settings and scenarios in which genetic testing is used (e.g. prenatal, diagnostic, cancer). These policies address the overarching coverage principles that broadly apply based on the purpose of the test. They also address specific use situations that may apply to many different tests (e.g. predictive testing for a known familial mutation).

Each of these overarching policies includes an inventory of all available test-specific policies that apply to that use. For example, the Pharmacogenomic Testing policy includes a list of all policies for tests that may be used to assess drug response or toxicity risk. Because tests can be used for multiple purposes, the same test-specific policy may be referenced by more than one Clinical Use Policy. However, when a test specific policy is not available, the overarching coverage principles found in these Clinical Use Policies may be applied.

Molecular and Genetic Test Specific Policies
The policies in this section address a test or group of tests that are used to assess some health condition. The purpose of these policies is to provide a framework for determining medical necessity and coverage determinations for a specific test, including where more limited testing may be supported by the medical evidence when broader testing is not. These policies provide background about each condition, the available tests, the scenarios in which the test may be used, and the evidence used to determine medical necessity criteria.

Index
Policies are organized by type (Clinical Use or Test Specific) and are arranged alphabetically in each section. Because a test may be referred to by many names (e.g., the gene, the method, the condition being tested), the index is intended to help the user cross reference policies, tests, and conditions located in this manual. A particular test, condition, or use may be covered in multiple policies within this manual.
Glossary
This glossary contains definitions for common genetics, medical and laboratory terminology

Administrative Policies
These policies define payment of claims for specific laboratory tests.

Limitations and Restrictions
When using this manual in electronic or printed form, the following restrictions apply:

- Evidence-based genetic testing is defined as the identification of targeted genetic sequences within the genome of an individual with clinically-identified risk factors or traits suspected of being specific to the genetic disorder, condition, or trait under investigation.

- The medical policies contained in this manual are the proprietary property of CareCore National, LLC, for use by its clients only. These medical policies may not be posted, shared, altered, cited or reproduced without the express written consent of CCN. Commercial use of these policies is prohibited.

- Medical policies are not to be considered medical advice for a specific patient. Policies are used in the process of determining whether a service may be medically necessary and eligible for coverage.

- Medical Policies are interpreted and applied at the sole discretion of the Health Plan.

- Current Procedural Terminology (CPT®) codes and descriptions are the property of the American Medical Association with all rights reserved.
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Molecular and Genetic Clinical Use Policies
Genetic Testing for the Screening, Diagnosis, and Monitoring of Cancer

Description

Genetic testing for screening, diagnosis and monitoring of cancer refers to molecular diagnostic tests whose purposes include identifying the possible presence of cancer in asymptomatic, average risk individuals; confirming the absence or presence of cancer; and monitoring the absence or presence of cancer after a prior diagnosis and treatment.

Screening

The goal of cancer screening is to identify the possible presence of cancer before symptoms appear. Screening tests cannot diagnose cancer, but typically determine if there is an increased chance cancer is present, and triages individuals for more invasive, diagnostic testing. Most cancer screening does not include genetic testing, but instead relies on physical exam, radiological exams, or non-genetic laboratory tests. Advances in human genetics, however, have identified several molecular diagnostic tests that may provide clues for early cancer detection.

Diagnosis

When cancer is suspected because of an abnormal screening test or symptoms, blood tests for tumor markers or molecular testing on tissue samples can aid in confirming a diagnosis of cancer. These tests may contribute information to helping the clinician understand prognosis and treatment options.

Monitoring

During treatment, or after an apparently successful treatment, active monitoring is often recommended to identify if the cancer is responding to treatment or has returned or spread, before any symptoms appear. Monitoring may include increased surveillance or routine blood tests for tumor markers, and increasingly, molecular genetic tests.

• Tests used to determine hereditary cancer risk are covered separately as Genetic Testing for Cancer Susceptibility and Hereditary Cancer Syndromes.
• This policy does not address drug response to cancer, or testing to determine which therapies to use. Please refer to Pharmacogenetic Testing for Drug Toxicity and Response for that purpose.
• This policy does not address diagnostic or predictive testing for conditions other than non-inherited cancer. Refer to Diagnostic Genetic Testing of a Symptomatic Patient for Diseases Other than Cancer and Predictive Genetic Testing or Risk Assessment for Diseases Other Than Cancer for those purposes.

Criteria: General Coverage Guidance

Individuals may be considered for genetic testing for screening, diagnosing, or monitoring cancer when ALL of the following conditions are met:
- **Technical and clinical validity**: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- **Clinical utility**: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

**Limits:**
- Testing will be considered only for the number of genes or tests necessary. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- For tests that look for changes in germline DNA (i.e., not tumor DNA or viral DNA), testing will be allowed once per lifetime per gene. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

**Criteria: Test-specific Policies**

Policies are available for the following tests designed to screen for, diagnose, or monitor cancer. See the individual policy documents arranged alphabetically by policy name in the *Test-specific Policies* section. For tests without a specific policy, use the General Coverage Guidance provided in Section 1.

- Bone Marrow Biopsy Chromosome Analysis
- CellSearch™
- Gene Expression Profiling for Cancers of Unknown Primary (CUP)
- GSTP1 Testing, Prostate Cancer
- PCA3 Testing, Prostate Cancer
- Prolaris®
- RET/PTC Rearrangement, Thyroid Cancer
- UroVysion®
Genetic Testing to Diagnose Non-Cancer Conditions

Description
Diagnostic testing is performed in patients with clinical signs or symptoms of a non-cancer genetic condition. The genetic test may confirm or rule out a clinical diagnosis. In some cases, genetic testing is the gold standard for making a diagnosis based on evidence- or consensus-based guidelines. In others, it may be used to confirm a clinical diagnosis, offer prognostic information that impacts management, or rule out a diagnosis in the differential. Often, diagnostic testing of an affected individual will offer results that are relevant to the testing of other family members.

- This policy does not include risk assessment or predictive testing for at-risk, asymptomatic individuals. Please refer to Predictive Genetic Testing or Risk Assessment for Diseases Other Than Cancer for that purpose.
- Diagnostic testing of a pregnancy or an embryo is covered by policies on Genetic Testing for Prenatal Screening and Diagnostic Testing and Preimplantation Genetic Diagnosis, respectively.
- In addition, testing for hereditary cancer syndromes is addressed separately under Genetic Testing for Cancer Susceptibility and Hereditary Cancer Syndromes.

Criteria: General Coverage Guidance
Individuals may be considered for diagnostic genetic testing when ALL of the following conditions are met:
- Clinical signs and symptoms in the individual are consistent with the diagnosis in question.
- Technical and clinical validity: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- Clinical utility: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- Reasonable use: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:
- Testing will be considered only for the number of genes or tests necessary to establish carrier status. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Diagnostic genetic testing will be allowed once per lifetime per condition. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

Criteria: Special Circumstances:
Diagnostic testing of a child to inform reproductive planning and testing for parents or testing for siblings
Diagnostic genetic testing may be requested in a symptomatic child with a known genetic condition. While diagnostic testing may not impact management of the affected child, the information gained from genetic testing may be needed to perform accurate carrier testing in the child’s parent(s) and/or genetic diagnosis in a sibling.

In these circumstances, diagnostic genetic testing in the child may be considered when **ALL** of the following conditions are met:

- The diagnosis of the disease in the affected child is **certain or highly probable** based on clinical signs and symptoms, history, imaging, and/or results of other laboratory testing.
- The results of the genetic test in the symptomatic child must be **required** in order to perform accurate carrier testing in the child’s parent(s) and/or genetic diagnosis in a sibling.
- **Technical and clinical validity**: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- **Clinical utility**: Healthcare providers can use the test results to provide informative genetic testing for the child’s parents and/or for a current or future at-risk pregnancy.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

**Limits:**
- Testing will be indicated only for the number of genes or tests necessary to establish the familial mutation(s). A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Diagnostic genetic testing will be allowed once per lifetime per condition. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

**Criteria: Test-specific Policies**

Policies are available for the following tests designed predict disease risk. See the individual policy documents arranged alphabetically by policy name in the *Test-specific Policies* section. For tests without a specific policy, use the General Coverage Guidance provided in Section 1.

- Alzheimer’s disease
- Alpha-1-Antitrypsin
- Angelman Syndrome
- Array CGH
- Ataxia Telangiectasia
- Bloom Syndrome
- Brugada Syndrome
- CADASIL
- Canavan
- Celiac Disease
- Cystic Fibrosis (includes Congenital Absence of the Vas Deferens)
- Charcot-Marie-Tooth
- Duchenne/Becker Muscular Dystrophy
- Dentatorubral-Pallidoluysian Atrophy (DRPLA)
- Factor II (Prothrombin)
- Factor V Leiden
- Fragile X Syndrome
- Gaucher Disease
- Hemochromatosis
- Hypertrophic cardiomyopathy
- Huntington Disease
- Long QT syndrome
- Niemann Pick Disease, Type C
- Rett Syndrome
- Spinocerebellar Ataxia
- Tay-Sachs Disease
Genetic Testing for Cancer Susceptibility and Hereditary Cancer Syndromes

Description

Genetic testing for cancer susceptibility and hereditary cancer syndromes is performed in people with known risk factors for an inherited form of cancer. Testing may be used in people diagnosed with cancer when there are “red flags” in the person’s personal medical and/or family history for a hereditary form. Predictive genetic testing may also be performed for this group of conditions, in people known to be at increased risk of developing an inherited condition based on their family history. A positive genetic test result increases the risk for cancer (types vary by the gene involved) and, therefore, impacts medical management decisions around screening, prevention, and treatment.

- Tests used to screen for or make a diagnosis of cancer are covered separately as Genetic Testing for the Screening, Diagnosis, and Monitoring of Cancer.
- This policy does not address diagnostic or predictive testing for conditions other than hereditary cancer. Refer to Diagnostic Genetic Testing of a Symptomatic Patient for Diseases Other Than Cancer and Predictive Genetic Testing or Risk Assessment for Diseases Other Than Cancer for those purposes.

Criteria: General Coverage Guidance

Individuals may be considered for genetic testing for hereditary cancer syndromes when ALL of the following conditions are met:

- Technical and clinical validity: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- Clinical utility: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- Reasonable use: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:

- Testing will be considered only for the number of genes or tests necessary to establish carrier status. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Genetic testing is indicated once per lifetime per condition. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

Criteria: Special Circumstances

The following policies address a group of tests that are used for similar purposes. Because a variety of tests may be used, but the circumstances that justify testing are the same, individual test-specific policies are not necessary.
Predictive testing for at-risk people with known familial mutations

The genetic mutation(s) associated with a hereditary cancer syndrome can often be defined in an affected family member, allowing for testing of at-risk relatives for those specific mutations. Testing for known familial mutations is reasonable when **ALL** of the following conditions are met:

- **The mutation(s) in the family have been clearly defined** by previous genetic testing and information about those mutations can be provided** to the testing lab.
- **Technical and clinical validity:** The test must be accurate, sensitive and specific to the familial mutations.
- **Clinical utility:** Healthcare providers can use the test results to provide significantly better medical care for the individual.
- **Reasonable use:** The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

**Limits:**

- Testing will be considered only for the known familial mutations when clinically possible.
- Predictive genetic testing is indicated once per lifetime per condition.
- Predictive genetic testing will be considered only for adult individuals (age 18 and over). Exceptions may be considered if there are medical management and/or significant psychosocial benefits to testing prior to adulthood.\(^1,2\)

**References**


**Criteria: Test-specific Policies**

Policies are available for the following hereditary cancer syndrome tests. See the individual policy documents arranged alphabetically by policy name in the *Test-specific Policies* section. For tests without a specific policy, use the General Coverage Guidance provided in Section 1.

- BRACAnalysis® Rearrangement Test (BART)
- Cowden syndrome (PTEN gene)
- Familial adenomatous polyposis (FAP) and attenuated FAP
- Familial Malignant Melanoma
- Fanconi Anemia, Group D1
- Hereditary Breast Ovarian Cancer Syndrome (HBOC)
- Li-Fraumeni syndrome (TP53 gene)
- Lynch Syndrome (Hereditary non-polyposis colorectal cancer, HNPCC)
- Microsatellite instability (MSI)/immunohistochemistry (IHC) tumor screening for hereditary non-polyposis colorectal cancer
- MUTYH-associated polyposis (MAP)
- Peutz-Jeghers syndrome (PJS)
Genetic Testing for Non-Medical Purposes

Description

While most traditional genetic tests are used to for clear medical purposes, advances in gene discovery and genetic testing technology allow laboratories to offer genetic testing for other uses. Testing for paternity, ancestry, and non-disease traits such as baldness and eye color may be highly accurate and interesting. However, because these kinds of tests are not useful for medical management in the vast majority of cases, they are typically excluded from consideration.

Criteria: General Coverage Guidance

Any genetic test that DOES NOT meet the following criteria is excluded from consideration:

- **Technical and clinical validity:** The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- **Clinical utility:** Healthcare providers can use the test results to provide significantly better medical care for the individual.
- **Reasonable use:** The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Criteria: Test-specific Policies

The following types of testing are specifically excluded from consideration:

- **Genome-wide association studies (GWAs):** testing a large number of genetic variations spread across the whole genome for disease associations, generally done for information outside of a specific clinical need or context
  - **Common** trade names: 23andMe, Navigenics, Pathway Genomics, deCODEme
- **Paternity testing:** testing to establish biological relationships, often between a father and child(ren) but sometimes to determine other kinds of relationships (siblings, grandparents, etc.)
- **Ancestry testing:** testing that helps people discover more about the genetic make-up of their ancestors, generally used by genealogists and those interested in family history
  - **Common** trade names: Ancestry.com, 23andMe, Pathway Genomics, Family Tree DNA, deCODEme
- **Non-disease trait testing:** testing for physical traits (e.g., eye color, hair color, male pattern baldness, cellulite) that do not have associated health problems, or can be deemed cosmetic in nature.
- **Nutritional:** testing for variations in metabolism pathways that may suggest vitamin or other nutritional supplements.
  - **Common** trade names: MyDNAVitamins, GeneWise
- **Athletic ability:** Testing to predict athletic performance types.
  - **Common** trade names: SportGene, Athleticode
- Genetic testing related to dating services
  - **Common** trade names: Scientific Match
Pharmacogenomic Testing for Drug Toxicity and Response

Click here for applicable Medicare NCD/LCD information

Description
For the purposes of this policy, pharmacogenomic tests are performed to assess a person’s response to therapy or risk for toxicity from drug treatment. Testing may be performed prior to treatment, in order to determine if the individual has genetic differences that could affect drug response and/or increase the risk for adverse drug reactions. Testing may also be performed during treatment, to assess whether an individual is having an adequate response or to investigate the cause of an unusual or adverse reaction.

Criteria: General Coverage Guidance
Pharmacogenomic tests may be indicated when ALL of the following conditions are met:

- The individual is currently taking or considering treatment with a drug that has an associated pharmacogenomic test.
- Technical and clinical validity: The test must be accurate, sensitive, and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- Clinical utility: Healthcare providers can use the test results to guide changes in drug therapy management.
- Reasonable use: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social, or ethical challenges.

Limits:
- Testing will be covered only for the number of genes or tests necessary to establish drug response. When available and cost-efficient, a tiered approach to testing, with reflex to more detailed testing and/or different genes, is recommended.
- For pharmacogenomic tests that look for changes in germline DNA (i.e., not tumor DNA or viral DNA), testing will be allowed once per lifetime per gene. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

Criteria: Special Circumstances
Exclusions
Coverage for some tests may be excluded from the plan’s benefit. These tests may be considered investigational or are not supported by existing evidence, professional guidelines and/or the FDA, or their use in medical management is deemed to be still evolving.

The following pharmacogenomic tests are typically not a covered benefit.

- 5HT2C (Serotonin Receptor) gene variants
- Ankyrin G gene variants
Pharmacogenomic

• COMT (Catechol Methyl Transferase) gene variants
• CYP450 gene variants (including, but not limited to CYP1A2, CYP2D6, CYP2C9, CYP2C19, CYP3A4, CYP3A5) for psychotherapeutic, cardiovascular, or general drug response
• DRD2 (Dopamine Receptor) gene variants
• KIF6 gene variants
• MTHFR gene variants
• NAT2 gene variants
• OPRM1 gene variants
• SLC6A4 (5-HTTLPR) serotonin transporter variants

Criteria: Test-specific Policies

Policies are available for the following pharmacogenomic tests. See the individual policy documents arranged alphabetically by policy name in the Test-specific Policies section. For tests without a specific policy, use the General Coverage Guidance provided in Section 1.

• BCR-ABL Transcript Level Testing
• BRAF Testing, Anti-EGFR Treatment Response
• CCR5 Tropism Testing
• CYP2C9 & VKORC1 for Warfarin Metabolism
• CYP2C19 for Clopidogrel Response
• CYP2D6 for Tamoxifen Metabolism
• DPD Deficiency Testing
• EGFR Mutation Analysis, NSCLC
• HLA-B*1502
• HLA-B*5701
• KRAS Testing, Anti-EGFR Treatment Response
• MammaPrint® Breast Cancer Assay
• Mammostrat® Breast Cancer Assay
• OncotypeDX Breast Cancer Assay
• OncotypeDX Colon Cancer Assay
• TPMT Testing
• UGT1A1 Testing

NCD/LCD Jurisdiction and CPT Codes

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<th>Required ICD9 Codes?</th>
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Pharmacogenomic Testing for Drug Toxicity and Response

CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV


81227 CYP2C9 GENE COM VARIANTS
81225 CYP2C19 GENE COM VARIANTS

No No Yes
81226 CYP2D6 GENE COM VARIANTS
81291 MTHFR GENE

FL, PR, VI
LCD: L33703

81227 CYP2C9 GENE COM VARIANTS
81225 CYP2C19 GENE COM VARIANTS
81226 CYP2D6 GENE COM VARIANTS
81291 MTHFR GENE

VA, NC, SC, WV
LCD: L33599

81225 CYP2C19 GENE COM VARIANTS
81226 CYP2D6 GENE COM VARIANTS
81291 MTHFR GENE

See LCD jurisdictions that refer to MolDX.

References


Genetic Testing to Predict Disease Risk

Description

Predictive genetic testing is performed in people known to be at increased risk of developing an inherited non-cancer condition (for the purposes of this policy) based on their family history. For some conditions, a positive genetic test predicts with certainty that the person will eventually develop signs and symptoms of a condition. For other conditions, a positive genetic test result indicates an increased risk (susceptibility) for a condition. A negative result may rule out a condition, or lower the risk significantly. Having test results may improve medical management through improved screening, preventive measures, prophylactic medication, and other means.

- This policy does not include testing of a symptomatic individual. Please refer to Diagnostic Genetic Testing of a Symptomatic Patient for that purpose.
- Predictive testing for hereditary cancer syndromes is addressed separately under Genetic Testing for Cancer Susceptibility and Hereditary Cancer Syndromes.

Criteria: General Coverage Guidance

Individuals may be considered for predictive genetic testing when ALL of the following conditions are met:

- The individual is known to be at-risk for developing inherited condition because a parent, sibling, or child is affected by or known to be a carrier of a genetic disease.
- Technical and clinical validity: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- Clinical utility: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- Reasonable use: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:

- Testing will be considered only for the number of genes or tests necessary to establish carrier status. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Predictive genetic testing will be allowed once per lifetime per condition. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.
- Predictive testing will be considered only for adult individuals (age 18 and over). Exceptions may be considered if there are medical management and/or significant psychosocial benefits to testing prior to adulthood.1,2
Criteria: Special circumstances

Testing for Known Familial Mutations

The genetic mutation(s) associated with a genetic disease can often be defined in an affected family member, allowing for testing of at-risk relatives for those specific mutations. Testing for known familial mutations may be considered when **ALL** of the following conditions are met:

- The mutations in the family have been **clearly defined** by previous genetic testing and **information about those mutations can be provided** to the testing lab.
- **Technical and clinical validity**: The test must be accurate, sensitive and specific to the familial mutations.
- **Clinical utility**: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:

- Testing will be considered only for the known familial mutations when clinically possible.
- Predictive genetic testing will be allowed once per lifetime per condition.
- Predictive testing will be considered only for adult individuals (age 18 and over). Exceptions may be considered if there are medical management and/or significant psychosocial benefits to testing prior to adulthood.  

References


Criteria: Test-specific Policies

Policies are available for the following tests designed to predict disease risk. See the individual policy documents arranged alphabetically by policy name in the *Test-specific Policies* section. For tests without a specific policy, use the General Coverage Guidance.

- Alzheimer’s disease
- Amyotrophic lateral sclerosis (ALS)
- CADASIL
- Charcot-Marie-Tooth neuropathy
- Duchenne/Becker Muscular Dystrophy
- Dentatorubral-Pallidoluysian Atrophy (DRPLA)
- Huntington Disease
- Hypertrophic cardiomyopathy
- Long QT syndrome
- Factor II (Prothrombin)
- Factor V LeidenSpinocerebellar Ataxia
Genetic Testing for Prenatal Screening and Diagnostic Testing

Description

Prenatal screening and diagnostic testing is performed during pregnancy to identify fetuses at increased risk for or affected with genetic conditions and birth defects. Screening with ultrasound and maternal serum markers is routinely offered. Prenatal diagnosis by chorionic villus sampling or amniocentesis for chromosome abnormalities is available to all women. However, it is usually offered specifically to those at higher risk because of maternal age, a positive screen result, abnormal ultrasound findings, or known risk of a genetic condition based on family history. Investigations for fetal infection and blood antigen incompatibility may also be performed in the prenatal period. Results of testing are used to guide reproductive decision-making, pregnancy management and anticipatory management of the infant at birth.

Note: This policy does not include prenatal or preconception carrier screening or preimplantation genetic testing. Please refer to Genetic Testing for Carrier Screening and Reproductive Planning and Preimplantation Genetic Diagnosis for those purposes.

Criteria: General Coverage Guidance

Individuals may be considered for genetic testing for prenatal screening and diagnostic testing when ALL of the following conditions are met:

- **Technical and clinical validity**: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- **Clinical utility**: Healthcare providers can use the test results to provide significantly better medical care and/or assist patients with reproductive planning.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:

- Testing will only be covered for the number of genes or tests necessary to establish a prenatal diagnosis. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Prenatal diagnostic testing will be allowed once per pregnancy. Exceptions may be considered if ambiguous results require retesting for clarification.

Criteria: Special Prenatal Diagnosis Circumstances

Each of the following policies addresses a group of tests that are used for similar purposes in pregnancy. Because a variety of tests may be used, but the circumstances that justify testing are the same, individual test-specific policies are not necessary.
Prenatal Diagnostic Testing Based on Family History

Prenatal genetic testing, generally by amniocentesis or CVS, for the diagnosis of a genetic condition is reasonable when the following conditions are met:

- The pregnancy is at an increased risk for a genetic disease because of ANY of the following:
  - At least one parent is known or suspected to be a carrier of a genetic condition based on the family history and/or previous carrier testing results; or
  - One or both parent(s) are affected with a genetic condition; or
  - A sibling is affected with a genetic condition; AND
- The genetic condition is associated with potentially severe disability or has a lethal natural history.

Fetal Infectious Disease Testing

Genetic testing may be used for the diagnosis of an infectious disease (e.g., cytomegalovirus, toxoplasmosis, parvovirus B19, and varicella zoster) in a fetus according to current guidelines from the American College of Obstetricians and Gynecologists (ACOG). Prenatal testing, generally by amniocentesis or CVS, is reasonable when ANY of the following conditions are met:

- Clinical signs and symptoms of a current infection in the mother; OR
- Serologic evidence of a current or recent infection in the mother (with or without clinical signs); OR
- Fetal abnormalities identified on ultrasound indicating an increased risk for a congenital infection

References


Blood Antigen Incompatibility Testing

Prenatal genetic testing, generally by amniocentesis, for the determination of blood antigen genotype is supported by current evidence-based recommendations from the American College of Obstetricians and Gynecologists.1 Fetal antigen genotyping is reasonable when the following conditions are met:

- A positive erythrocyte antibody screen in the mother; AND EITHER
  - The father’s blood antigen genotype is known and indicates a risk for the fetus to be positive; OR
  - The father’s blood antigen genotype is not known and unavailable

References


Criteria: Test-specific Policies

Policies are available for the following prenatal diagnostic tests. See the individual policy documents arranged alphabetically by policy name in the Test-specific Policies section. Note that prenatal diagnosis may be just one of several test uses addressed in the same policy (e.g., a policy such as Canavan Disease may address diagnostic, carrier, and prenatal diagnostic testing). For tests without a specific policy, use the General Coverage Guidance provided in Section 1 above.
- Aneuploidy FISH
- Ataxia Telangiectasia
- Bloom Syndrome
- Canavan Disease
- Cystic Fibrosis
- Fragile X Syndrome
- Gaucher Disease
- Niemann Pick Disease, Types A and B
- Niemann-Pick Disease, Type C
- Prenatal Diagnosis, Chromosome Abnormalities
- Prenatal Maternal Serum Screening
- Rett Syndrome
- Spinocerebellar Ataxia, Types 1, 2, 3, 6, 7, 12, and 17
- Tay-Sachs Disease
Genetic Testing for Carrier Status

Description

Carrier screening is performed to identify genetic risks that could impact reproductive decision-making for parents or prospective parents. Carriers are generally not affected but have an increased risk to have a child with a genetic condition. Carrier screening may be available for autosomal recessive conditions, X-linked conditions, and certain chromosome abnormalities. Ideally, carrier screening is performed prior to pregnancy so that a full range of reproductive options are available to an at-risk couple. However, in practice, it is often performed early in pregnancy when prenatal care is established.

- This policy does not include prenatal or preimplantation genetic testing. Refer to policies on Genetic Testing for Prenatal Screening and Diagnostic Testing and Preimplantation Genetic Diagnosis for those purposes.
- In addition, testing that may identify carriers who have clinical signs and symptoms (e.g., cystic fibrosis testing for men with congenital absence of the vas deferens, fragile X genetic testing for women with premature ovarian failure) is addressed as Diagnostic Genetic Testing of a Symptomatic Patient For Conditions Other Than Cancer.

Criteria: General Coverage Guidance

Individuals may be considered for genetic testing for carrier screening when ALL of the following conditions are met:

- **Technical and clinical validity**: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- **Clinical utility**: Healthcare providers can use the test results to provide significantly better medical care and/or assist individuals with reproductive planning.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:

- Testing will only be considered for the number of genes or tests necessary to establish carrier status. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Carrier testing will be allowed once per lifetime. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.
- Carrier testing is indicated only in adults. Carrier screening in minor children is not indicated, except in the case of a pregnancy of the minor child.

Routine Carrier Screening

Individuals may be considered for routine carrier screening when testing is supported by evidence-based guidelines from governmental organizations and/or well-recognized professional societies in the United States.
Carrier Screening Based on Family History

Individuals may be considered for carrier screening based on a family history of a genetic condition when ALL of the following conditions are met in addition to the general criteria above:

- The diagnosis of a genetic condition in a family member is known.
- The parent(s) or prospective parent(s) are at-risk to be carriers of that condition based on the pattern of inheritance.
- The genetic condition is associated with potentially severe disability or has a lethal natural history.

Partner Testing of Known Carrier or Affected Individuals

Individuals may be considered for carrier screening if their partners are known carrier or affected individuals when all of the following conditions are met in addition to the general criteria above:

- The diagnosis of a genetic condition or carrier status in the partner is known.
- The genetic condition is associated with potentially severe disability or has a lethal natural history.

Criteria: Special Situations

Exclusions

Multiplex Carrier Screening

Multiplex carrier screening tests are designed to identify carrier status or predict risk for many genetic diseases (70 or more) in a single test. Several multiplex carrier screening tests are available now. Others are known to be in development and will come to market in the next few years. Each test has a unique set of diseases included in novel and proprietary genetic testing platforms.

Of the genetic conditions included in the currently available multiplex carrier screening tests, 12 of them are recommended for at least some people based on ethnicity by either the American College of Obstetrics and Gynecology (ACOG) and/or the American College of Medical Genetics (ACMG). However, mutation analysis is not the preferred initial screening test for some.

These tests do not meet the criteria above for technical and clinical validity and clinical utility:

- The technologies used by the multiplex carrier screening tests are novel. Information about the test's performance, if available, is often provided completely by the laboratory marketing the test, which could be subject to bias.
- Some of the commonly included tests, such as beta-thalassemia and Tay-Sachs disease, have inexpensive and reliable screening tests available (CBC with RBC indices and hexosaminidase A enzyme activity, respectively) that are superior to genetic testing.
- Multiplex carrier screening tests typically include carrier screening for many diseases that have not been identified as appropriate for population-based carrier screening. They may also include disorders, such as hereditary hemochromatosis and factor V Leiden, which affect primarily adults and are generally manageable. These kinds of conditions do not meet the requirements for reproductive carrier screening programs.
Criteria: Test-specific Policies

Policies are available for the following tests designed to predict carrier status. See the individual policy documents arranged alphabetically by policy name in the Test-specific Policies section. For tests without a specific policy, use the General Coverage Guidance provided in Section 1.

Carrier screening for:

- Ashkenazi Jewish Diseases
- Ataxia Telangiectasia
- Bloom Syndrome
- Canavan Disease
- Cystic Fibrosis
- Duchenne/Becker Muscular Dystrophy
- Fragile X syndrome
- Gaucher Disease
- Hemoglobinopathies (alpha-thalassemia, beta-thalassemia, and sickle cell disease)
- Niemann Pick Disease, Types A and B
- Tay-Sachs Disease
Investigational and Experimental Molecular/Genomic Testing

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* - Clinical Review necessary prior to authorization for this procedure.
† - Additional information may be required upon claim receipt.

Click here for applicable Medicare NCD/LCD information

Description

Molecular and genomic (MolGen) tests are routinely released to market that make use of novel technologies or have a novel clinical application. These tests are often available on a clinical basis long before the evidence base required to support clinical validity and utility is established. Because these tests are often proprietary, there may be no independent test evaluation data available in the early stages to support the laboratory’s claims regarding test performance and utility.

An experimental or investigational procedure is generally defined as the use of a service, supply, drug or device that is not recognized as standard medical care for the condition, disease, illness or injury being treated as determined by the health plan based on independent review of peer reviewed literature and scientific data. Investigational and experimental (I&E) MolGen tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition. In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

As new MolGen tests become commercially available, the evidence base is reviewed. Tests determined to be investigational/experimental by the Health Plan are catalogued in this policy. When the evidence base for any test becomes significant enough, a separate, test-specific policy will be created. MolGen tests determined to be investigational and/or experimental are excluded from coverage. Note that a single CPT/HCPCS code may describe more than one MolGen test. Some tests under a single code may be covered while others are determined to be I&E.

Criteria

This section catalogues some, but not all, molecular and genomic tests that have been determined to be investigational or experimental. I&E tests may also be addressed in test-specific policies and the reader is referred to those documents for additional information. Given the rate of new tests becoming clinically
available, tests that will be I&E may not yet be addressed in this policy but such decisions will be made upon individual case review.

**Novel Oncology Molecular/Genomic Tests**

The following tests used in the screening, diagnosis, prognostication, and/or treatment decision-making for various neoplasms are not covered.

**Gene Expression Assays:**

- **BluePrint Molecular Subtyping Profile** [Proprietary 80-gene expression signature to classify Basal-type, Luminal-type and ERBB2-type breast cancers by Agendia]
- **Breast Cancer Index(SM) (BCI)** [Proprietary biomarker profile to assess distant breast cancer recurrence from BioTheranostics]
- **ColonSentry** [Proprietary 7-gene signature to detect colorectal cancer from GeneNews]
- **ColoPrint** [Proprietary 18-gene signature to assess colon cancer recurrence risk from Agendia]
- **Decipher assay** [proprietary 22 RNA biomarker assay to assess prostate cancer risk post surgery from GenomeDx Biosciences]
- **DecisionDx-GBM assay** [Proprietary metagene expression assay to predict glioblastoma response to the first-line standard of care treatment from Castle Biosciences]
- **DecisionDx-Melanoma assay** [Proprietary 31-gene signature to assess melanoma metastatic risk from Castle Biosciences]
- **DecisionDx-Thymoma assay** [Proprietary 9-gene signature to assess thymoma metastatic risk from Castle Biosciences]
- **DecisionDx-UM assay** [Proprietary 15-gene signature to assess uveal/ocular melanoma metastatic risk from Castle Biosciences]
- **MammaPrint** [Proprietary 70-gene signature to assess breast cancer distant recurrence risk from Agendia]
- **Mammostrat** [Proprietary 5-gene biomarker panel that estimates recurrence risk for some breast cancers from Clarient]
- **miRInform Thyroid** [Proprietary 17-gene expression assay to identify thyroid nodule malignancy from Interpace Diagnostics]
- **MyPRS Plus testing** [Proprietary 70 gene expression profile designed to predict prognosis of myeloma from Signal Genetics]
- **OncotypeDX Breast Cancer Assay DCIS** [Proprietary 12-gene expression assay to predict the risk of DCIS local recurrence from Genomic Health]
- **OncotypeDX Colon Cancer Assay** [Proprietary 12-gene expression assay to assess colon cancer recurrence risk from Genomic Health]
- **OncotypeDX Prostate Cancer Assay** [Proprietary 17-gene expression assay to predict more or less favorable prostate cancer pathology from Genomic Health]
- **Pervenio Lung RS Test** [Proprietary 14-gene expression assay for risk stratification of early stage NSCLC from Life Technologies]
- **Prolaris** [Proprietary 46-gene expression signature to predict prostate cancer prognosis from Myriad Genetics]
- **Symphony Profile** [Combination of four proprietary Agenda breast cancer tests]
Other Novel Assays:

- ArgusCyte Breast Health Test [Proprietary test to detect circulating breast cancer tumor cells (CTC) and molecular treatment target expression in nipple aspirate fluid from Atossa Genetics]
- CellSearch Circulating Tumor Cell Test [FDA-cleared system to capture and enumerate CTCs]
- CertNDx Hematuria Testing [Proprietary test from Predictive Biosciences assessing FGFR3, MMP2, TWIST1 and NID2]
- CertNDx Molecular Grading [Proprietary test from Predictive Biosciences assessing FGFR3 and Ki-67 IHC]
- CertNDx Recurrence Testing [Proprietary test from Predictive Biosciences assessing FGFR3, MMP2, Vimentin and NID2]
- ConfirmMDx for Prostate Cancer [Proprietary DNA methylation assay to distinguish true negative biopsies by MDxHealth]
- DecisionDx-G-CIMP assay [Proprietary DNA methylation assay of nine CpG islands in eight genes to predict survival based on standard of care management of glioma from Castle Biosciences]
- ForeCyte Breast Health Test [Proprietary test to detect small numbers of abnormal cells in nipple aspirate fluid as an adjunct to mammography from Atossa Genetics]
- Knowerror [Proprietary test for DNA based specimen provenance confirmation by Strand Diagnostics]
- miRInform Pancreas Test [Proprietary score based on expression levels of seven microRNAs to differentiate pancreatic ductal adenocarcinoma from chronic pancreatitis provided by Asuragen]
- NADiA ProsVue [Proprietary nucleic acid detection immunoassay designed to determine the rate of change of serum total prostate specific antigen over time to predict prostate cancer recurrence risk from Iris Personalized Medicine]
- Ova1 [Proprietary five biomarker panel to predict malignancy risk of gynecological mass from Vermillion] CPT code 81503
- PathFinderTG [Proprietary topographic genotyping assay to be used when a definitive pathologic diagnosis cannot be made from RedPath Integrated Pathology]
- PAULA [Proprietary panel of six biomarkers designed to detect lung cancer in asymptomatic individuals at high risk from Genesys Biolabs]
- Previsstage GCC Colorectal Cancer Staging Test [Proprietary GCC/GUCY2C gene expression test to detect metastatic colorectal cancer from DagnoCure]
- Prezeon [Proprietary PTEN loss of function test to predict more aggressive disease with several cancers from Myriad Genetics]
- Prostate Core Mitomic Test [Proprietary test using mitochondrial DNA to detect prostate cancer not identified by standard biopsy pathology from Mitomics]
- ProstaVysion [Proprietary panel of two biomarkers designed to predict prostate cancer prognosis from Bostwick Laboratories]
- ROMA Risk of Ovarian Malignancy Algorithm [Proprietary test using the combination of CA125 + HE4 antigens to assess the likelihood of malignancy before surgery; test kit
from Fujirebio Diagnostics, Inc. and offered by several reference laboratories] CPT code 81500

- **Rosetta Kidney Cancer Test** [Proprietary microRNA-based assay that differentiates 4 main histological types of primary kidney tumors from Rosetta Genomics]
- **Rosetta Lung Cancer Test** [Proprietary microRNA-based assay that identifies four main subtypes of lung cancer from Rosetta Genomics]
- **Rosetta Mesothelioma** [Proprietary microRNA-based assay that differentiates malignant pleural mesothelioma from carcinomas in the lung and pleura from Rosetta Genomics]
- **Skin DNA Mitomic Test** [Proprietary test using mitochondrial DNA to detect prostate cancer not identified by standard biopsy pathology from Mitomics]
- **Sun Exposure Mitomic Test** [Proprietary test to screen for level of sun-related DNA damage from Mitomics]
- **VeriStrat** [Proprietary eight peak protein signature designed to classify NSCLC prognosis as good or poor from biodesix]

**Cancer of Unknown Primary Testing**, Including:

- **CancerTYPE ID** [Proprietary 92-gene molecular classifier by BioTheranostics]
- **ResponseDX Tissue of Origin Test** [Proprietary microarray based gene expression diagnostic from Response Genetics]
- **Rosetta Cancer Origin Test** [Proprietary microRNA-based test for 49 identifiable origins of metastatic tumors from Rosetta Genomics]

**Cardiovascular Molecular/Genomic Tests**

The following tests used to predict cardiovascular disease and/or direct therapy are not covered.

- 4q25-AF Risk Genotype Test (rs2200733 allele)
- 9p21 Genotype Test (rs10757278 and rs1333049 alleles)
- Apolipoprotein E Genotype
- C-GAAP (Clopidogrel Genetic Absorption Activation Panel) [Proprietary test from Transgenomic Lab, includes ABCB1 and CYP2C19 gene variants]
- KIF6 Genotype Test
- LPA-Aspirin Genotype Test (4399Met allele)
- LPA-Intron 25 Genotype Test
- Methylene tetrahydrofolate Reductase (MTHFR) (677C>T and 1298A>C gene variants) – CPT code 81291
- Statin Induced Myopathy Genotype (SLCO1B1)

**Gene Variant or Marker Risk Assessment Tests**

The following tests that make use of inherited genomic information to assess disease risk, prognosis, or subtyping are not covered.

- **ARiSK Autism Risk Assessment Test** [Proprietary test from IntegraGen]
• **BREVAGen** [Proprietary sporadic breast cancer risk based on genetic markers by Phenogen Sciences]
• **Cardiac Health Insight** [Proprietary test from Pathway Genomics that assesses genetic markers for a cardiac-related conditions]
• **Crohn's prognostic test** [NOD2/CARD15 gene variant testing]
• **Eyedox genetic test** [Proprietary test to type/subtype and determine severity of color vision deficiency from Genevolve]
• **Health Conditions Insight** [Proprietary test from Pathway Genomics that assesses genetic markers for a variety of health conditions]
• **IBD sgi Diagnostic** [Proprietary test from Prometheus with genomic components including ATG16L1, STAT3, NKX2-3, and ECM1 gene variants.]
• **LactoTYPE** [Proprietary test from Prometheus that assesses the hypolactasia C/T genetic variant]
• **Macula Risk** [Proprietary test from ArcticDx to predict risk of age-related macular degeneration progression]
• **Methylenetetrahydrofolate Reductase** (MTHFR) (677C>T and 1298A>C gene variants)
• **Pathway Fit** [Proprietary test from Pathway Genomics that focuses on metabolism, diet, and exercise traits]
• **RetnaGene AMD** [Proprietary test from Sequenom CMM to predict risk of wet AMD progression]
• **ScoliScore** [Proprietary test for progressive and protective genes designed to estimate the risk for adolescent idiopathic scoliosis progression from Transgenomic] – CPT code 0004M
• **Skin DNA Mitomic Test** [Proprietary test for MC1R gene variants to predict increased susceptibility to UV radiation from Mitomics]

### Whole Exome/Whole Genome Sequencing

CPT codes 81415, 81416, 81417, 81425, 81426, 81427

- **ClariView Exome** [Claritas Genomics]
- **EmExome** [Emory Genetics Laboratory]
- **Exome Sequencing with Symptom-Guided Analysis** [ARUP]
- **First-Tier Exome** [Ambry Genetics]
- **Whole Exome Sequencing** [Baylor Medical Genetics Laboratories]
- **XomeDx/XomeDxPlus: Whole Exome Sequencing** [GeneDX]

### Pharmacogenomic Panels

- **Drug Response (Medication) Insight** [Proprietary test from Pathway Genomics ]
- **Genecept Assay** [Proprietary panel of biomarker tests to predict response to different psychiatric treatments from Genomind]
- **GeneSightRx ADHD** [Proprietary test from AssureRx assessing three genes]
- **GeneSightRx Analgesic** [Proprietary test from AssureRx assessing two genes]
- **GeneSightRx Psychotropic** [Proprietary test from AssureRx assessing six genes]
- **TheraGuide 5-FU** [Proprietary panel of DPYD and TYMS gene variants to assess risk of 5-fluorouracil toxicity from Myriad Genetics]
Non-cancer Gene Expression Assays

- **Corus CAD** [Coronary artery disease risk proprietary test from XDx Expression Diagnostics]
- **Renal Transplant Monitoring (FOXP3, Granzyme B, Perforin, IP10)** [Gene expression panel that is an indirect indicator of immune response designed to detect or monitor renal transplant rejection from Quest Diagnostics]
- **VectraDA** [Proprietary panel of 12 biomarkers that yields a rheumatoid arthritis disease activity score from Crescendo Bioscience]

+ Addressed in test-specific policy

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Molecular and Genetic Test-Specific Policies
Afirmà Gene Expression Classifier

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<th>Requires:</th>
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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

What Is the Afirmà Gene Expression Classifier for Thyroid Cancer?

- The Afirmà test is based on a gene expression classifier that uses FNA samples for determining the risk of malignancy in thyroid nodules previously diagnosed as cytologically indeterminate (i.e. not clearly benign or malignant) that would otherwise be recommended for diagnostic thyroid surgery.¹
- Palpable thyroid nodules are often evaluated using fine needle aspiration (FNA) to rule out malignancy. In 15-30% of cases, the result is indeterminate.² Cytologically indeterminate nodules may then be referred for diagnostic surgery; however, 70-80% have benign results.³,⁴
- In order to help avoid unnecessary diagnostic surgeries, gene expression testing may be used to further characterize these nodules as benign or suspicious for cancer.
- The Afirmà test is intended for cytologically indeterminate FNA biopsy samples including atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), and follicular or Hürthle Cell Neoplasms.⁵
- When indicated, the Afirmà test must be used in conjunction with cytopathology, ultrasound assessment, and other clinical factors to determine a patient’s risk of thyroid cancer and the necessity of thyroid surgery.⁵
- Afirmà test results correlate with the postoperative surgical pathology,⁶ which may guide the decision to observe the patient’s nodule in lieu of surgical resection.⁶

Test Information

- Full Afirmà testing may include a combination of cytopathology and gene expression testing. This policy addresses only the gene expression testing component.
  - An FNA sample can be submitted for cytopathology assessment.
  - If the cytopathology diagnosis is benign or malignant, the analysis is complete.
  - If the cytopathology diagnosis is indeterminate, the Gene Expression Classifier is performed.
- The Afirmà Gene Expression Classifier test measures the gene expression levels of 142 genes from FNA biopsy specimens.¹ These 142 genes are correlated with histologically benign thyroid nodules that were previously diagnosed as cytologically indeterminate in two prospective multicenter clinical validation studies.⁵,⁷ A retrospective multicenter study confirmed originally published Afirmà Gene Expression Classifier test performance.⁸
- The Afirmà test result is reported as benign or suspicious for malignancy.¹
○ An Afirma benign result has a negative predictive value of 95% (i.e. a risk of malignancy of 5% or less).
○ Afirma Suspicious for Malignancy results have a positive predictive value for malignancy of 38%.

Guidelines and Evidence

- The National Comprehensive Cancer Network (NCCN, 2014) Thyroid Carcinoma Guidelines incorporate the use of molecular tests in the evaluation of indeterminate thyroid nodules. For FNA results consistent with Follicular or Hürthle Cell Neoplasms, or Atypia of undetermined significance/Follicular lesion of undetermined significance (AUS/FLUS) with a “High clinical suspicion of malignancy”, they state:
  ○ "Molecular diagnostics may be useful to allow reclassification of follicular lesions (i.e., follicular neoplasm, Hürthle cell neoplasm, atypia of undetermined significance (AUS), follicular lesions of undetermined significance (FLUS)) as they are more likely to be benign or more likely to be malignant...If molecular testing predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less), consider observation."

Criteria

- Testing Multiple Samples:
  ○ The Afirma test is reimbursed only once per date of service, and
  ○ The Afirma test is indicated only once per thyroid nodule per lifetime.
- Required Clinical Characteristics:
  ○ Afirma Gene Expression Classifier testing is indicated for thyroid nodules with indeterminate FNA results that are included in the following cytopathology categories*:
    ▪ Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), or
    ▪ Follicular or Hürthle Cell Neoplasm, and
  ○ The patient is not undergoing thyroid surgery for diagnostic confirmation.
- Required Testing Process:
  ○ If FNA of a nodule is indicated to evaluate for malignancy, and the sample is sent to Veracyte for cytopathology, the gene expression classifier is only indicated when the result is indeterminate, and
  ○ Supporting documentation of an appropriate indeterminate cytology result will be required for payment.

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<th>Test-Specific Criteria?</th>
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*CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV

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References

Alpha-1-Antitrypsin Deficiency

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**Alpha-1-antitrypsin deficiency SERPINA1 (serpin peptidase inhibitor) gene analysis, common variants (e.g., *S and *Z)**

* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

**Description**

- Alpha-1 antitrypsin deficiency (AATD) is inherited in an autosomal recessive manner. It results from mutations in the SERPINA1 gene, which codes for the enzyme alpha-1 antitrypsin (AAT).²
- It is estimated that 1 in 5000 to 1 in 7000 people in North America have AATD.¹ However, AATD is an under recognized condition, with estimates that only about 10% of those affected are actually diagnosed.³
- The most common clinical manifestation is chronic obstructive pulmonary disease (COPD), particularly emphysema.¹⁻³ Smoking is a major environmental risk factor for lung disease in AATD, increasing the risk for emphysema by 1000-fold.²
- AATD also increases the risk for neonatal/childhood liver disease (manifested by obstructive jaundice and hyperbilirubinemia) and early onset adult liver disease (usually cirrhosis and fibrosis).¹
- AATD testing includes identifying reduced serum levels of alpha-1 antitrypsin in combination with either:
  - Protease Inhibitor (PI) typing by isoelectric focusing to determine phenotype (PI*Z, PI*S).¹ PI typing is considered the "gold standard" for diagnosing AATD, as it can detect normal as well as variant alleles except null alleles;¹⁻³ OR
  - Genetic testing for the two common mutations in the SERPINA1 gene (Z and S), which make up greater than 95% of the mutations.¹
- The Z allele is by far the most common and more severe variant.²
- If PI typing is ambiguous, mutation testing should be performed.¹
- The American Thoracic Society and the European Respiratory Society (2003) statement on the Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency states that testing for AATD is recommended for the following indications (quoted directly):²
  - Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators
  - Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly
  - Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g., cigarette smoking, occupational exposure)
  - Adults with necrotizing panniculitis
  - Siblings of an individual with AATD

---

*Click here for applicable Medicare NCD/LCD information*
Criteria

Consideration for alpha-1 antitrypsin deficiency (AATD) testing is determined according to diagnostic guidelines from the American Thoracic Society.2

Testing may be considered in individuals who meet ANY of the following criteria:

- Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators; OR
- Individuals of any age with unexplained liver disease; OR
- Asymptomatic individuals with persistent obstruction on pulmonary function tests who have identifiable risk factors (e.g., cigarette smoking, occupational exposure); OR
- Adults with necrotizing panniculitis; OR
- Siblings of an individual with AATD

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Alzheimer’s Disease

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**Description**

Alzheimer’s Disease (AD) is characterized by adult-onset dementia and personality changes. It usually begins with memory failure and can include confusion, aggression, Parkinsonian features and other features. Early onset AD usually occurs before age 65. Fewer than 2% of patients with AD test positive for APP, PSEN1 or PSEN2 genes. Treatment for AD is individualized, based upon the symptoms with which the patient is presenting. Some medications have been found to slow the progression of AD, however, at this time no treatment or cure has been found to stop or reverse symptoms.

Genetic testing: Genetic testing is not approved for Alzheimer’s Disease including but not limited to APOE, PSEN1, PSEN2, or APP testing because it is considered experimental, investigational or is unproven.

**Criteria**

Genetic testing is not approved for Alzheimer’s Disease including but not limited to APOE, PSEN1, PSEN2, or APP testing because it is considered experimental, investigational or is unproven.

**References**

Amyotrophic Lateral Sclerosis

<table>
<thead>
<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Procedure Code(s)</th>
<th>Requires:</th>
<th>Lab Procedure Restrictions†</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD1 testing for ALS</td>
<td>81404</td>
<td>Yes</td>
<td>No</td>
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</table>

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† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Description

Amyotrophic lateral sclerosis (ALS) is a neurological disease caused by the progressive degradation of motor neurons (nerve cells that control voluntary muscle movement).1 ALS initially presents as muscle weakness, twitching, cramping, or slurred speech.1 Symptoms then worsen and include muscle atrophy and difficulty swallowing1, with death usually related to failure of the respiratory muscles.

The majority of ALS cases are sporadic, but some familial forms have been identified. About 20% of familial ALS cases are caused by mutations in the SOD1 gene.1 The SOD1 gene encodes superoxide dismutase, an enzyme whose function remains unclear.1,2 SOD1-related ALS is usually inherited in an autosomal dominant fashion. First-degree relatives (parents, siblings, children) of affected individuals have a 50% chance of also having the mutation.1-3 Predictive testing for SOD1 mutations is endorsed by consensus-based guidelines from the European Federation of Neurological Societies (EFNS)4, which state: "Pre-symptomatic genetic testing should only be performed in first degree adult blood-relatives of patients with a known SOD1 gene mutation. Testing should only be performed on a strictly volunteer basis."

Identifying a SOD1 mutation in a pre-symptomatic individual can impact future management and overall prognosis of ALS, but is considered controversial because of reduced penetrance (not everyone with a mutation will necessarily develop symptoms), lack of overall intervention or prevention strategies, and inability to predict the age of onset.1,2

The EFNS guidelines outline a presymptomatic testing protocol similar to those for other late-onset neurologic conditions for which no specific disease treatment is available, including appropriate genetic counseling.4 The potential psychosocial impact of test results on the individual and the family should be considered, and the possibility of discrimination in regards to insurance coverage, employment, and education should be reviewed.1,4

Criteria

Predictive genetic testing may be considered when an individual has a first-degree relative (parent, sibling, child) affected with SOD1-related ALS, that relative has had SOD1 genetic testing, and the family mutation is known.

Predictive genetic testing for ALS, by SOD1 or other gene testing, in the absence of a known familial mutation is specifically excluded by policy.
References


Aneuploidy FISH

<table>
<thead>
<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Procedure Code(s)</th>
<th>Requires: Prior-authorization</th>
<th>Lab Procedure Restrictions†</th>
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<tr>
<td>Fluorescence in situ hybridization (FISH) testing for common chromosome abnormalities (chromosomes 13, 18, 21, X, Y)</td>
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<td>88275</td>
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</table>

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Description

Individuals may be considered for standard fluorescence in situ hybridization (FISH) testing for chromosomes 13, 18, 21, X and Y (“aneuploidy FISH”) on a fetal tissue sample (i.e., chorionic villus sample, amniocentesis) according to current evidence-based guidelines from the American College of Obstetricians and Gynecologists (ACOG). The advantage of FISH analysis is turnaround time: results are available in days, rather than the weeks needed to obtain a karyotype.

Criteria

Testing with aneuploidy FISH is allowed once per pregnancy AND only when a result is needed in less than one week in order to exercise some pregnancy management option AND at least one of the following indicate an increased risk for a chromosome abnormality:

- Screening result suggests Down syndrome or trisomy 18
- Advanced maternal age
- One major or at least two minor fetal structural defects found on ultrasound
- Previous fetus or child with aneuploidy
- Parent of this pregnancy has a structural chromosome abnormality (e.g., translocation, inversion) involving chromosome 21, 13, 18, X, or Y
- Parent of this pregnancy has an extra chromosome (e.g., Down syndrome, XXX syndrome, Klinefelter syndrome)

References

Angelman Syndrome

<table>
<thead>
<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Procedure Code(s)</th>
<th>Requires:</th>
<th>Prior-authorization*</th>
<th>Lab Procedure Restrictions†</th>
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<tr>
<td>Methylation Analysis</td>
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<tr>
<td>Chromosome and Deletion Analysis of UBE3A</td>
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<tr>
<td>Imprinting defect analysis</td>
<td>Research testing only</td>
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<td>UBE3A Sequence analysis</td>
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</table>

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Click here for applicable Medicare NCD/LCD information

Description

Angelman syndrome (AS) is a microdeletion syndrome characterized by severe developmental delay and speech development, ataxic gait, and a demeanor that includes frequent laughing, smiling and excitability. Other common features include microcephaly (small head size) and seizures. At birth, individuals with AS have typical birth weight, head circumference, and infant development. The diagnosis of AS can be delayed as symptoms tend not to develop until 6 months of age, with typical characteristics. Developmental delays begin to be noticed at six months of age, while seizures tend to develop between one and three years of age. The average child with AS will walk between 2½ and 6 years of age, and typically has an ataxic gait. Approximately 10% of individuals are never ambulatory. AS may originally be suspected in a toddler because of gross motor and speech delay. Individuals with AS have a normal lifespan but independent living is not possible. Once AS has been diagnosed, an individual should be assessed for communication needs including communication aids and sign language. Control of seizures is also important.

In 2005 a group of scientists and clinicians with experience with Angelman syndrome convened to update an original consensus statement about the clinical features of Angelman syndrome. The updated consensus statement discusses the clinical features not previously part of the diagnostic process, diagnosis and testing for Angelman syndrome.

One gene – UBE3A - is associated with Angelman Syndrome. Several alterations can disrupt the normal production of UBE3A. This includes deletions, paternal uniparental disomy (the inheritance of two paternal 15 chromosomes), or imprinting defects. Deletions can arise from either spontaneous microdeletions or a deletion from an inherited chromosomal translocation. Microdeletions are the cause of 65-75% of AS cases. Parental translocations and insertions can result in a deletion of the AS region, but are not a significant cause (approximately 1%) of AS patients. Paternal uniparental disomy (UPD) is the reason for
an additional 3-7% of AS cases. Approximately 3% of cases have an imprinting defect within the imprinting center (IC) where the imprint inherited from the paternal chromosome is unable to be reset. Individuals inheriting the IC defect from their father are asymptomatic, whereas those inheriting the defect from their mother have AS. The remaining 3-11% of cases result from mutations in the UBE3A gene. More than 60 mutations have been found in this gene. There have been limited genotype-phenotype correlations, with deletions having more severe symptoms regarding microcephaly, seizures, hypopigmentation, motor difficulties and language deficiencies. Individuals with UPD and imprinting defects have better growth, lower prevalence of seizures, less motor difficulties and better language development with some individuals developing minimal spoken language.

AS is seen in approximately 1 in 12,000 to 1 in 20,000 individuals. The risk for siblings being affected depends on the cause of AS. The risk to sibs can be <1% in the case of microdeletions, most cases of paternal UPD, and imprinting defects without a deletion in the imprinting center (IC). The risk could be as high as 50% in cases of chromosome translocations or insertions, imprinting defects with a deletion or UBE3A mutation. Lastly, the risk could be as high as 100% should a father have 15:15 Robertsonian translocation which is rare.

Diagnosis of AS occurs in a stepwise fashion. Initial testing will confirm the diagnosis and direct the testing to detect the cause of AS. To confirm a diagnosis of AS in an individual, DNA methylation analysis should be performed first. An abnormal methylation analysis will identify approximately 80% of individuals with AS. If the methylation analysis is normal, the next step is to conduct a sequence analysis of the UBE3A gene. If the methylation analysis is abnormal, a deletion/duplication analysis of the UBE3A gene region can identify microdeletions through FISH or chromosomal microarray (CMA). If a microdeletion is not found, step-wise testing should be for chromosome 15 UPD and then for mutations in the imprinting center (IC) of UBE3A.

If a deleterious mutation has been identified in the IC, relatives of affected individuals can be tested. The risk to a sibling of a proband with AS can be as high as 50% if the mother has an IC deletion. Genetic counseling should be offered to at-risk family members in a family where a germline UBE3A mutation has been identified. The risk to a sibling of a proband can be as high as 50% if the mother has a UBE3A mutation. Early detection of at-risk individuals allows for counseling regarding risks to offspring, preimplantation testing and prenatal testing. Genetic testing can be performed on amniocytes obtained through amniocentesis or chorionic villi obtained through chorionic villus sampling.

Criteria

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

Methylation Analysis for Angelman Syndrome, Molecular Analysis

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous methylation analysis, AND
• Diagnostic Testing for Symptomatic Individuals:
  o Developmental delay, typically severe to profound, without loss of milestones, and
  o Movement or balance disorder, typically with ataxia, and
  o Frequent laughter/smiling, apparent happy demeanor; easily excitable personality (often with uplifted hand-flapping, or waving movements), or hypermotoric behavior, and
  o Speech impairment with no or minimal number of words, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

Duplication/Deletion Analysis for UBE3A

• Genetic Counseling
  o Pre and post-test counseling by a medical geneticist or genetic counselor, AND
• Previous Testing:
  o Methylation analysis results are abnormal, and
  o No previous duplication/deletion analysis, AND
• Diagnostic Testing for Symptomatic Individuals:
  o Developmental delay, typically severe to profound, without loss of milestones, and
  o Movement or balance disorder, typically with ataxia, and
  o Frequent laughter/smiling, apparent happy demeanor; easily excitable personality (often with uplifted hand-flapping, or waving movements), or hypermotoric behavior, and
  o Speech impairment with no or minimal number of words
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

Uniparental Disomy Analysis

• Genetic Counseling
  o Pre and post-test counseling by a medical geneticist or genetic counselor, AND
• Previous Testing:
  o Methylation analysis results are abnormal, and
  o Duplication/Deletion analysis is negative, AND
• Diagnostic Testing for Symptomatic Individuals:
  o Developmental delay, typically severe to profound, without loss of milestones, and
  o Movement or balance disorder, typically with ataxia, and
  o Frequent laughter/smiling, apparent happy demeanor; easily excitable personality (often with uplifted hand-flapping, or waving movements), or hypermotoric behavior, and
  o Speech impairment with no or minimal number of words, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

Imprinting Center Defect Analysis

• Genetic Counseling
  o Pre and post-test counseling by a medical geneticist or genetic counselor, AND
• Previous Testing:
  o Methylation analysis results are abnormal, and
  o Previous UPD testing is negative, AND
• Diagnostic Testing for Symptomatic Individuals:
  o Developmental delay, typically severe to profound, without loss of milestones, and
  o Movement or balance disorder, typically with ataxia, and
  o Frequent laughter/smiling, apparent happy demeanor; easily excitable personality (often with uplifted hand-flapping, or waving movements), or hypermotoric behavior, and
  o Speech impairment with no or minimal number of words, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

**UBE3A Sequence Analysis**

• Genetic Counseling
  o Pre and post-test counseling by a medical geneticist or genetic counselor, AND
• Previous Testing:
  o Methylation analysis results are normal, and
  o No previous sequencing of UBE3A, AND
• Personal History:
  o Developmental delay, typically severe to profound, without loss of milestones, and
  o Movement or balance disorder, typically with ataxia, and
  o Frequent laughter/smiling, apparent happy demeanor; easily excitable personality (often with uplifted hand-flapping, or waving movements), or hypermotoric behavior, and
  o Speech impairment with no or minimal number of words, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

**Family Mutation Testing**

• Genetic Counseling
  o Pre and post-test counseling by a medical geneticist or genetic counselor, AND
• Previous Testing:
  o No previous UBE3A testing, AND
• Family History:
  o Familial UBE3A mutation known in blood relative, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

Testing is authorized for known family mutation(s) only.

<table>
<thead>
<tr>
<th>NCD/LCD Jurisdiction and CPT Codes</th>
<th>Specific Tests</th>
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<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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<td>FL, PR, VI</td>
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</table>
Angelman Syndrome

References

# Ashkenazi Jewish Disease Carrier Screening

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<thead>
<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Procedure Code(s)</th>
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<th>Lab Procedure Restrictions</th>
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<tr>
<td>Canavan disease gene analysis (ASPA, aspartoacylase), common variants (eg, E285A, Y231X)</td>
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<td>Maple syrup urine disease gene analysis (BCKDHB, branched-chain keto acid dehydrogenase E1, beta polypeptide), common variants (eg, R183P, G278S, E422X)</td>
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<tr>
<td>Bloom syndrome gene analysis (BLM), common variant (2281del6ins7 variant)</td>
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<td>Cystic fibrosis gene analysis (CFTR, cystic fibrosis transmembrane conductance regulator), common variants (eg, ACMG/ACOG recommended panel)</td>
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<tr>
<td>Fanconi anemia, type C gene analysis (FANCC, Fanconi anemia, complementation group C), common variant (eg, IVS4+4A&gt;T)</td>
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<tr>
<td>Glycogen storage disease, Type 1a, von Gierke disease gene analysis (G6PC, glucose-6-phosphatase, catalytic subunit), common variants (eg, R83C, Q347X)</td>
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<td>Gaucher disease gene analysis (GBA, glucosidase, beta, acid), common variants (eg, N370S, 84GG, L444P, IVS2+1G&gt;A)</td>
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<tr>
<td>Tay-Sachs disease gene analysis (HEXA, hexosaminidase A), common variants (eg, 1278insTATC, 1421+1G&gt;C, G269S)</td>
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<td>Familial dysautonomia gene analysis (IKBKAP, inhibitor of kappa light polypeptide gene enhancer in B-cells kinase complex-associated protein), common variants (eg, 2507+6T&gt;C, R696P)</td>
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<td>Mucolipidosis, type IV gene analysis (MCOLN1, mucolipin 1), common variants (eg, IVS3-2A&gt;G, del6.4kb)</td>
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<td>Niemann-Pick disease, Type A gene analysis (SMPD1, sphingomyelin phosphodiesterase 1, acid lysosomal), common variants (eg, R496L, L302P, fsP330)</td>
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<tr>
<td>Unlisted molecular pathology procedure (Used for testing various less common disorders)</td>
<td>81479</td>
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</table>

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Carrier screening is widely available for at least 11 genetic disorders that are more common and/or have superior mutation detection rates in the Ashkenazi Jewish population. The American College of Obstetrics and Gynecology (ACOG)\(^1\) and the American College of Medical Genetics (ACMG)\(^2\) recommend carrier screening for a group of disorders when at least one member of a couple is Ashkenazi Jewish and that couple is pregnant or planning pregnancy.

Both organizations agree that testing should be offered for cystic fibrosis, Canavan disease, familial dysautonomia, and Tay-Sachs disease. ACMG also recommends routine testing for Fanconi anemia, Niemann-Pick disease, Bloom syndrome, mucolipidosis IV, and Gaucher disease.\(^2\) Maple syrup urine disease and glycogen storage disease 1a carrier screening for common Ashkenazi Jewish mutations is now clinically available, but not addressed in current carrier screening guidelines. These two tests meet the criteria for additional carrier screening set in the 2008 ACMG guidelines.\(^2\)

Criteria

Testing may be considered for carrier screening for all or any desired subset of the Ashkenazi Jewish genetic diseases when BOTH of the following are met:

- The individual is planning a pregnancy or currently pregnant; AND
- At least one partner of a couple is Ashkenazi Jewish
  - NOTE: Detection rates for testing are higher in people with Ashkenazi Jewish ancestry. If only one partner of a couple is Ashkenazi Jewish, testing should start in that person when possible.

Testing may be considered for carrier screening of a single Ashkenazi Jewish disease, regardless of ethnicity or reproductive plans, if EITHER of the following are met:

- The individual has a family history of one of these conditions; OR
- The individual’s partner is a known carrier or affected with any of these conditions

<table>
<thead>
<tr>
<th>NCD/LCD Jurisdiction and CPT Codes</th>
<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
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<td>81255 HEXA GENE</td>
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<td>81290 MCOLN1 GENE</td>
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<td>81330 SMPD1 GENE COMMON VARIANTS</td>
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For FL, PR, VI:
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For VA, NC, SC, WV:
LCD: L33599 ([link](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33599&ContrId=234&ver=27&ConDate=&DocId=L33599&SearchType=Advanced&bc=KAAAAAgAAAAAAA%3d%3d&))

See LCD jurisdictions that refer to MolDX.

LCD: MolDX ([link](http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Excluded%20Tests~94PMVC2103?open&navmenu=Browse*By*Topic|))

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<tr>
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See LCD jurisdictions that refer to MolDX.
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<td>81209</td>
<td>BLM GENE</td>
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References

Ataxia-Telangiectasia (A-T) is a progressive neurological disorder affecting children under the age of 5. Symptoms of A-T include truncal and gait ataxia, ocular apraxia and slurred speech usually between the ages of 3-5. Head tilting after the age of 6 months can also be noted. Between 85-95% of individuals have elevated alpha-fetoprotein (AFP) levels (NORD, Perlman). The disease is progressive such that by age 10 most individuals utilize a wheelchair. Conjunctival telangiectasias can appear several years after the onset of neurological symptoms and can also be seen on the neck and ears. The disease is also characterized by immunodeficiencies, malignancies, and radiation sensitivity. Although individuals with A-T live to adulthood, they are at an increased risk for early death. Currently, most individuals live beyond 25 years, with some surviving into their 50s. Cause of death is associated with A-T associated cancers, infection, and pulmonary failure.

Approximately 60-80% of individuals with A-T have immunodeficiencies; one-third of individuals have severe immunodeficiencies, another third have moderate deficiencies and the remainder is without documented deficiency. Additionally, about 30% of affected individuals develop cancer during their lifetime. Most of the cancers are blood disorders including leukemias or lymphomas, accounting for ~85% of malignancies. However, non-lymphoid cancers including gastric, breast, basal cell, ovarian, liver, uterine and melanoma are also seen. Cancer treatment can be complicated because of radiation sensitivity.

One gene, ATM, is associated with A-T. More than 600 mutations have been found in this gene, with several genotype/phenotype observations noted. Specifically, one mutation found mainly in the Turkish population and several other mutations found in a limited number of individuals have been associated with slower neurological progression, later onset of symptoms, little-to-no cancer risk, or milder phenotype and longer lifespan. Additional populations that are associated with specific mutant alleles include: African American, Amish, Costa Rican, Iranian, Italian, Japanese, North African Jewish, Norwegian, Polish, and Utah Mormon.

A-T is inherited in an autosomal recessive inheritance pattern, found in approximately 1 in 40,000 to 1 in 100,000 live US births. The carrier frequency is estimated at 1%. It is the most common cause of childhood progressive cerebellar ataxia in most countries. Portugal and Japan may have a higher prevalence of ataxia with oculomotor apraxia (AOA), and several populations have specific alleles associated more frequently with their A-T populations. For autosomal recessive conditions, the parents of an affected child are obligate (definite) carriers of at least one ATM mutation, and siblings of an affected
individual have a 50% chance of being a carrier, and a 25% chance of being affected with A-T. Individuals with A-T typically do not reproduce, but if they should, each child would inherit an ATM mutation and be an obligate carrier for A-T.

ATM has been implicated as a candidate gene for an increased risk for breast cancer, especially in women with a strong family history of breast cancer.1-4, 8-11, 14-16, 22, 23 Epidemiological data has also suggested an increased risk for cardiovascular disease in carriers as well.15 Therefore, carriers of ATM mutant alleles may need to be screened for breast cancer and cardiovascular disease. At least one study suggests that haplotype screening could be used to identify ATM mutations in individuals diagnosed with breast cancer.5 Heterozygous ATM mutations have also been found in some patients with T-cell prolymphocytic leukemia (T-PLL)24, B-cell chronic lymphocytic leukemia (B-CLL),25, 26 and mantle cell lymphoma.27

Diagnosis of A-T can occur through targeted mutation analysis of the ATM gene, sequence analysis of the ATM gene, deletion analysis of the ATM gene, or linkage/haplotype analysis. Targeted mutation analysis is available for individuals with a known familial mutation. It is also available for individuals of certain backgrounds where specific mutations are found more frequently. Campbell et al. suggests that SNP haplotyping may be able to prescreen for the mutation to be targeted by sequencing in about 30% of newly diagnosed individuals, especially if the individual belongs to a well-studied ethnic or religious group5, although genetic testing laboratories are not routinely doing this. Sequence analysis can identify ~90-95% of A-T mutations. Deletion/duplication analysis can identify another 1-2% of mutations.6, 7 Linkage or haplotype analysis can be utilized when mutations are not found in affected individuals.

Once a deleterious mutation has been identified, relatives of affected individuals can be tested. Genetic testing should be offered to at-risk family members in a family where a germline ATM mutation has been identified. Detection of at-risk individuals affects medical management in the case of breast cancer screening and cardiovascular disease screening. Prenatal testing is available to individuals with a known family mutation. Genetic testing can be performed on amniocytes obtained through amniocentesis or chorionic villi obtained through a chorionic villus sampling. At this time, general population-wide carrier screening for A-T is not recommended.

The Eighth International Workshop on Ataxia-Telangiectasia was convened in 1999. The workshop described ATM mutations and cancer risk in heterozygotes, and potential therapeutic approaches. Genetic testing strategies were not described.10

Genetic testing is approved to confirm a diagnosis or carrier status in anyone who meets clinical criteria for A-T. Individuals meeting clinical criteria for A-T testing will undergo sequence analysis. Deletion/duplication testing is offered to those meeting the criteria and have tested negative through sequence analysis. Additionally, genetic testing is approved to determine the carrier status in an at risk relative with a known family mutation. Individuals with a family member with a known A-T mutation(s) should be tested for that/those mutation(s).

Criteria

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.
**Known ATM Family Mutation Testing**

- **Genetic Counseling:**
  - Pre and post-test counseling by a medical geneticist, genetic counselor or neurologist, AND
- **Previous Genetic Testing:**
  - No previous genetic testing of ATM, AND
- **Carrier Screening Individuals:**
  - Known family mutation in ATM in 1st, 2nd, or 3rd degree biologic relative(s), OR
- **Prenatal Testing for At-Risk Pregnancies:**
  - ATM mutations identified in both biologic parents.

**ATM Full Sequence Analysis**

- **Clinical Consultation & Genetic Counseling:**
  - Examination by a geneticist, oncologist, or neurologist family with hereditary ataxias, and
  - Pre and post-test counseling by a medical geneticist or genetic counselor, AND
- **Previous Genetic Testing:**
  - No previous ATM gene sequencing, and
  - No known ATM mutation in family, AND
- **Diagnostic Testing for Symptomatic Individuals:**
  - Elevated Alpha-fetoprotein (AFP) levels, or
  - Decreased ATM protein detected by immunoblotting, and
  - Progressive cerebellar ataxia, or
  - Truncal and gait ataxia, or
  - Oculomotor apraxia, OR
- **Diagnostic Testing for Carriers:**
  - One mutation detected by targeted mutation analysis, and
  - Elevated Alpha-fetoprotein (AFP) levels, or
  - Decreased ATM protein detected by immunoblotting, OR
- **Testing for Individuals with Family History or Partners of Carriers:**
  - 1st, 2nd, or 3rd degree relative diagnosed with Ataxia-Telangiectasia clinical diagnosis, family mutation unknown, and testing unavailable, or
  - Partner is monoallelic or biallelic for ATM mutation, and
  - Has living children with this partner, or
  - Has the potential and intention to reproduce, OR

**ATM Duplication/Deletion Analysis†**

- **Clinical Consultation & Genetic Counseling:**
  - Examination by a geneticist, oncologist, or neurologist family with hereditary ataxias, and
  - Pre and post-test counseling by a medical geneticist or genetic counselor, AND
- **Previous Genetic Testing:**
  - No previous deletion/duplication analysis of ATM, and
  - No mutations detected in full sequencing, or
Heterozygous for mutation and elevated alpha-fetoprotein levels or decreased ATM protein detected by immunoblotting.

**Lab Testing Restrictions:** Testing is authorized after no mutations detected with full sequence analysis.

**References**


19. Atlas Genetics Oncology, Available at: [http://atlasgeneticsoncology.org/Genes/ATM123.html](http://atlasgeneticsoncology.org/Genes/ATM123.html)


23. Byrnes et al. Are the so called low penetrance breast cancer genes, ATM, BRIP1, PALB2 and CHEK2, high risk for women with strong family histories? Breast cancer research 2008;10:208. Available at: breast-cancer-research.com/content/10/3/208.
BCR-ABL Transcript Level Testing

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</table>

* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Click here for applicable Medicare NCD/LCD information

Description

Imatinib (Gleevec®), nilotinib (Tasigna®), and dasatinib (Sprycel®) are oral cancer drugs in a class called tyrosine kinase inhibitors (TKIs). Treatment response to these drugs can be monitored by measuring BCR-ABL transcripts. CML practice guidelines from the National Comprehensive Cancer Network recommend molecular level monitoring of BCR-ABL transcripts for disease progression/response in individuals with CML.

Criteria

BCR-ABL transcript level testing is indicated in individuals at the initiation of treatment and at regular intervals (ranges from every month to once every 3-6 months) during treatment with ANY of the following drug therapies:

- Imatinib (Gleevec®)
- Nilotinib (Tasigna®)
- Dasatinib (Sprycel®)
LCD: L24308 (http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=24308&ContrId=359&ver=73&ContrVer=1&Date=&DocID=L24308&SearchType=Advanced&bc=KAAAAAgAAAAAAA%3d%3d&)

81403 MOPATH PROCEDURE  BCR/ABL fusion gene  No  Yes (Group 5)
LEVEL 4

See LCD jurisdictions that refer to MolDX.

LCD: MolDX (http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse^By^Topic|||)

81401 MOPATH PROCEDURE  ABL1 (c-abl oncogene 1)  No  No  N/A
LEVEL 2

81403 MOPATH PROCEDURE  ABL1 (c-abl oncogene 1)  No  No  N/A
LEVEL 4

References

Bloom Syndrome

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<td>BLM targeted mutation analysis of Ashkenazi Jewish mutation (blmAsh mutation)</td>
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<td>BLM full sequencing analysis</td>
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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specific sequence to be followed or additional information is required and must be supplied by the lab performing procedure(s) for full claim payment.

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Description

Bloom syndrome (BSyn) is an autosomal recessive condition caused by mutations in BLM and is characterized by severe pre and postnatal growth deficiency, sparseness of subcutaneous fat tissue throughout infancy and early childhood, and short stature throughout postnatal life.1 Many affected individuals also have sun-sensitivity, causing a typical skin lesion to occur on the nose and cheeks.2-8 Individuals with BSyn are at an increased risk for immunodeficiency and developing cancer. The mean age of death is 27 years of age, with the most common cause of death being cancer.6 While BSyn is seen in all ethnicities, it primarily affects individuals in the Ashkenazi Jewish population.9-11

Because BSyn is recessive, individuals typically do not have other affected family members. Parents of affected individuals are obligate carriers; therefore siblings have a 50% chance of being carriers and a 25% chance of being affected. Carriers of BSyn are asymptomatic and do not exhibit any features of the condition. The carrier frequency in the general population is unknown, however, in the Ashkenazi population the carrier frequency is approximately is 1 in 107 (~1%).3,4,7,12

Diagnosis of BSyn occurs through cytogenetic testing of blood cells or cultured fibroblasts (skin cells), or molecular testing of BLM.13 Cytogenetically, the condition is diagnosed when a high frequency of chromosome breaks and rearrangements are seen in culture.4,5,13 While cytogenetics can be used to confirm a diagnosis of Bloom syndrome in an individual who is affected with BSyn, molecular testing must be used to confirm carrier status of an at-risk relative. Molecular testing is performed to confirm a cytogenetic diagnosis in an individual exhibiting symptoms, which allows other family members to be screened for the identified mutation(s). To date, there are 64 separate deleterious mutations that have been found in BLM – with blmAsh and c.2407dupT being the most common. The most common genetic mutation in Ashkenazi populations is blmAsh.3-5,7,12,14

Preventive use of genetic testing on a population wide basis, for any condition, may be cost-effective if genotypic information can be shown to predict disease risk. Population-wide screening is ethically justifiable only if there is an efficacious and cost-effective intervention to prevent the disorder in those who are identified as being at increased risk. Therefore, population wide carrier screening for BSyn is not recommended unless an individual is of Ashkenazi Jewish descent.7 Targeted mutation analysis of BLM is
available as a single multiplex assay for individuals of Ashkenazi Jewish descent. The Ashkenazi Jewish panel targets mutations associated with several autosomal recessive conditions with increased prevalence in this population. This can be practical from a convenience and cost perspective. However, an individual should be consented for each condition in the panel. If an individual does not consent to being tested for a particular condition, then each test should be ordered individually. Please see the Ashkenazi Jewish Screening Panel policy for more information.

Once a deleterious mutation has been identified, relatives of affected individuals can be tested. Individuals who are at risk for having a child with BSyn can have prenatal testing of their fetus. Prenatal testing is available and is can be performed through cytogenetic testing or mutation analysis, if both parental mutations are known.

Individuals diagnosed with BSyn should undergo early screening for both breast and colon cancer. Additionally, unexplained signs and symptoms that could possibly be explained by malignancy should be investigated immediately. Lastly, individuals diagnosed with BSyn should avoid sun exposure, and possibly receive reduced levels of radiation and DNA-damaging chemicals when being treated for a malignancy or other illness.

The American College of Medical Genetics (ACMG) supports offering carrier testing for Bloom syndrome to individuals of Ashkenazi Jewish descent for the common blmAsh mutation. It is anticipated that the detection rate will be >95%. This test should be offered to individuals of reproductive age, preferentially prior to pregnancy, with genetic counseling performed by a geneticist or genetic counselor. Counseling should include the following: 1) a description of the condition, 2) discussion of carrier risk associated with a negative test result, 3) the risk of passing the gene onto future offspring, and 4) discussion of the implications of a positive test on other family members. ACMG supports the testing of individuals of Ashkenazi Jewish descent, even when their partner is non-Ashkenazi Jewish. In this situation, testing would start with the individual who is Jewish and if blmAsh mutation is detected, sequencing of BLM in the non-Ashkenazi Jewish partner would follow.

The American College of Obstetrics and Gynecologists (ACOG) recommends those individuals considering a pregnancy or are pregnant should consider testing if at least one member of the couple is Ashkenazi Jewish or has a relative with BSyn. If the woman is pregnant, testing may need to be conducted on both partners simultaneously in order to receive results in a timely fashion. If one or both partners are found to be carriers of BSyn, genetic counseling should be provided and prenatal testing offered, if appropriate.

Genetic testing is indicated to confirm a diagnosis in anyone who meets the clinical criteria for Bloom syndrome, or to determine carrier status in an at-risk relative (such as individuals who have a family member with a known BLM mutation(s)). Individuals who meet clinical criteria for Bloom syndrome should undergo targeted mutation analysis of the common mutations first; if no mutations are detected, sequence analysis should follow. Finally, individuals of Ashkenazi Jewish descent should be offered carrier testing of the common blmAsh mutation (c.2281del6ins7). Those with a previous Ashkenazi Jewish screening panel, which contains this targeted mutation analysis, should not be authorized for repeat mutation detection for blmAsh. Additionally, sequence analysis is not necessary if the blmAsh mutation is not found in an asymptomatic individual of Ashkenazi Jewish descent.
Criteria

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

**Known BLM Family Mutation(s) Testing**

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing of BLM, AND
- Carrier Screening:
  - Known family mutation in BLM identified in 1st, 2nd, or 3rd degree biologic relative(s), OR
- Prenatal Testing for At-Risk Pregnancies:
  - BLM mutation identified in both biologic parents, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**BLM Targeted Mutation Analysis for Ashkenazi Mutation (c.2207_2212delinsTAGATTC “blmAsh” mutation)**

Ashkenazi Jewish individuals are recommended to have the full AJ Panel regardless of symptoms of disease. See Ashkenazi Jewish Disease Carrier Screening policy.

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous BLM genetic testing, including AJ screening panels containing targeted mutation analysis for blmAsh, AND
- Carrier Screening:
  - Ashkenazi Jewish descent, and
  - Have the potential and intention to reproduce, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Criteria

**BLM Full Sequencing Analysis**

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous BLM full sequencing, and
  - No known BLM mutation in biologic relative, and
o If Ashkenazi Jewish, targeted mutation analysis performed and no mutation detected or one mutation detected, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Unexplained severe intrauterine growth retardation that persists throughout infancy and childhood (< 5th percentile), or
  o An unusually small individual (<5th percentile) who develops erythematous skin lesions in the “butterfly area” of the face after sun exposure, or
  o An unusually small individual (<5th percentile) who develops a malignancy, OR

• Testing for Individuals with Family History or Partners of Carriers:
  o 1st, 2nd, or 3rd degree biologic relative with BSyn clinical diagnosis, family mutation unknown, and testing unavailable, or
  o Partner is monoallelic or biallelic for BLM mutation, and
  o Have the potential and intention to reproduce, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

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<th>Test-Specific Criteria?</th>
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See LCD jurisdictions that refer to MolDX.


| 81479 UNLISTED MOLECULAR PATHOLOGY | Ashkenazi Jewish Mutation Analysis Panels | No | No | N/A |
| 81209 BLM GENE                      |                                           | No | No | N/A |
References

Bone Marrow Biopsy Chromosome Analysis

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<td>Bone Marrow Biopsy Chromosome Analysis</td>
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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Description

Chromosome analysis – also called karyotyping – allows the chromosomes inside a cell to be visualized. This technique detects any changes from normal that are large enough to be seen microscopically, including rearrangements, duplications, and deletions. Acquired chromosomal changes are common in leukemia, lymphoma, and other hematological disorders. These chromosome abnormalities can be diagnostic and/or prognostic.

The National Comprehensive Care Network considers chromosome analysis of a bone marrow biopsy to be standard of care in the evaluation of acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), multiple myeloma, myelodysplastic syndromes, and Burkitt’s lymphoma.

Criteria

Chromosome analysis on a bone marrow biopsy meets criteria without further review when performed in the evaluation of leukemia, lymphoma, and other hematological disorders.

References

BRAF Testing, Anti-EGFR Treatment Response

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<th>Procedure Code(s)</th>
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<tr>
<td>BRAF mutation analysis for cetuximab (Erbitux®) and panitumumab (Vectibix®) colorectal cancer treatment response</td>
<td>81210</td>
<td>Investigational and Experimental</td>
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Description

Cetuximab (Erbitux®) and panitumumab (Vectibix®) are drugs specifically targeted to human epidermal growth factor receptor (anti-EGFR) used in the treatment of advanced colorectal cancer. Previous studies suggested that tumors with a mutation in either the KRAS gene (see the KRAS testing policy for details) or the BRAF gene will not respond to anti-EGFR therapy. However, more recent data suggests that the clinical utility of BRAF V600E testing is unclear. Colon cancer practice guidelines from the National Comprehensive Cancer Network state that BRAF testing in reflex to normal KRAS results prior to any EGFR therapy may be considered, but that “there are insufficient data to guide the use of anti-EGFR therapy in the first line setting with active chemotherapy based on BRAF V600E mutation status.”

Criteria

BRAF mutation testing is considered investigational and experimental due to NCCN guidelines stating that this testing is optional and not of clear clinical benefit in decision-making regarding the use of anti-EGFR agents.

References

BRAF V600 Tumor Marker Testing

<table>
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<th>Lab Procedure Restrictions</th>
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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

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Description

- BRAF is part of a cell signaling pathway that helps control cell growth. Mutations in the BRAF gene can cause out of control cell growth, which may lead to cancer. The most common BRAF mutation is called V600E (previously known as V599E), which accounts for about 70-90% of mutations in this gene.
- About 40-60% of cutaneous melanomas have a V600E BRAF mutation.
- Vemurafenib (Zelboraf®) is an orally-administered kinase inhibitor that is able to block the function of the V600E-mutated BRAF protein. It is specifically indicated for the treatment of patients with metastatic or unresectable melanoma whose tumors have a BRAF V600E mutation. It is not recommended for use in patients with wild type BRAF melanoma.
- Dabrafenib (Tafinlar®), a BRAF inhibitor, is approved to treat patients with advanced or unresectable melanoma whose tumors express the BRAF V600E gene mutation.
- Trametinib (Mekinist®), a MEK inhibitor, is approved to treat patients with advanced or unresectable melanoma whose tumors express the BRAF V600E or V600K gene mutations.

Test Information

- Vemurafenib was approved for use along with an FDA approved companion diagnostic developed by Roche molecular diagnostics called the cobas® 4800 BRAF V600 Mutation Test. The cobas 4800 BRAF V600 mutation test was clinically validated in the trials conducted for approval of vemurafenib. This testing specifically checks for the V600E mutation in formalin-fixed, paraffin-embedded melanoma tumor tissue.
- In 2013, dabrafenib and trametinib were approved for use along with an FDA approved companion diagnostic developed by Roche molecular diagnostics called the THxID BRAF test. The THxID BRAF test was clinically validated in the clinical studies supporting the approval of dabrafenib and trametinib.
- Several molecular diagnostic laboratories also perform BRAF V600E and V600K mutation analysis by laboratory-developed methods. These laboratory-developed tests may vary in the specimen type required, methodology used, mutations tested, sensitivity, and other test-specific data. At this time, no commentary is available from the FDA on the use of lab testing outside of the approved kit.
Guidelines and Evidence

- The US Food and Drug Administration (FDA) approved vemurafenib in August 2011 with a companion diagnostic:2
  - Confirmation of BRAF V600E mutation using an FDA approved test is required for selection of patients appropriate for ZELBORAF® therapy. The efficacy and safety of ZELBORAF® have not been studied in patients with wild-type BRAF melanoma."
- The National Comprehensive Cancer Network (NCCN, 2012) added vemurafenib as an option for the treatment of advanced or metastatic melanoma. The guidelines state: "Vemurafenib is recommended for patients with the V600 mutation of the BRAF gene documented by a CLIA-approved facility."4
- In stage III randomized controlled trials, vemurafenib was associated with a 63% relative reduction in the chance of death and a 74% relative reduction in the risk of tumor progression in people with previously untreated, unresectable or metastatic melanoma with the BRAF V600E mutation.1 An overall survival rate of 84% was seen in the vemurafenib group, compared to 64% in those on standard dacarbazine at 6 months (n=672).1
- The National Comprehensive Cancer Network (NCCN, 2014) added dabrafenib and trametinib as options for treatment of advanced or metastatic melanoma which require companion diagnostic testing. The guidelines state "Vemurafenib, dabrafenib, and trametinib are recommended only for patients with a V600 mutation of the BRAF gene documented by an FDA-approved or Clinical Laboratory Improvement Amendments (CLIA)-approved facility.”
- No other applications of BRAF testing have similarly strong evidence and are therefore not covered.

Criteria

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

Testing may be considered in individuals who meet the following criteria:
- Individual has been diagnosed with metastatic or unresectable melanoma, and
- At least one of the following treatment is being considered: Zelboraf® (vemurafenib), Tafinlar® (dabrafenib), or Mekinist® (trametinib), and
- BRAF V600 testing has not been performed previously

Exclusions

BRAF V600E tumor marker testing is not currently indicated as a companion diagnostic or for therapy selection for any other tumor types and is therefore not covered for these uses.
81210 BRAF GENE  Yes  Yes  No  
CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV
LCD: L33541  
84999 CLINICAL CHEMISTRY  Cobas 4800 BRAF V600  Yes  No  Yes  
TEST  81210 BRAF GENE  No  No  Yes  
DE, DC, MD, NJ, PA
LCD: L34796  
81210 BRAF GENE  Yes  Yes  No  
FL, PR, VI
LCD: L33703  
81210 BRAF GENE  No  No  N/A  
VA, NC, SC, WV
LCD: L33599  
81210 BRAF V600 Mutation Test  Yes  Yes  N/A  
See LCD jurisdictions that refer to MolDX.
LCD: MolDX  
81210 BRAF GENE  No  No  N/A  
LCD: MolDX  
81210 BRAF V600 Mutation Test  Yes  Yes  N/A  
References
2. Vemurafenib (ZELBORAF™) prescribing information. August 2011. Available at:  
5. Dabrafenib (Tafinlar®) prescribing information. May 2013. Available at:  
us.gsk.com/products/assets/us_tafinlar.pdf
6. Trametinib (Mekinist®) prescribing information. May 2013. Available at:  
# Breast Cancer Prognosis (MammaPrint 70 Gene Signature)

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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Click here for applicable Medicare NCD/LCD information

## What Is MammaPrint?

- MammaPrint is a 70-gene expression test designed to predict the chance of later-in-life recurrence of breast cancer in women with newly diagnosed, early stage breast cancer.\(^1\) It is FDA cleared for use along with other standard prognostic methods, such as disease staging, grading and other tumor marker analyses.\(^2\)
- MammaPrint is intended to assist patients and providers considering treatment with adjuvant chemotherapy. Patients assigned a "low risk" may choose hormone therapy (tamoxifen) alone and forego chemotherapy. Patients assigned a "high risk" may benefit from more aggressive treatment and choose to do chemotherapy.\(^1\)
- MammaPrint is designed for women with breast cancer who have:\(^1,2\)
  - Stage I or II invasive carcinoma
  - Tumor size <5.0 cm
  - Node-negative (no metastasis to lymph nodes)
  - Estrogen receptor-positive (ER+) or -negative (ER-) disease

## Test Information

- MammaPrint uses a microarray platform to analyze the expression level of 70 genes in the tumor. These 70 genes are thought to be critical in the cellular pathways to cancer metastasis.\(^1\)
- Based on the test results, patients are assigned either a low risk or a high risk for a distant recurrence. Low risk corresponds to a 10% risk of recurrence by 10 years without any additional adjuvant treatment. In contrast, those in the high risk group have a 29% risk of recurrence by 10 years without any additional adjuvant treatment.\(^1\)

## Guidelines and Evidence

- The **National Comprehensive Cancer Network (NCCN) 2014** Clinical Practice Guidelines for Breast Cancer state that:\(^3\)
  - The 21-gene RT-PCR assay (OncotypeDX) can be considered for patients with ER-positive, node-negative tumors measuring >0.5 cm in the management algorithm.
"A recent comparison of simultaneous analyses of breast cancer tumors using five different gene-expression models indicated that four of these methods (including Mammaprint and Oncotype DX) provided similar predictions of clinical outcomes."[NCCN p. MS-21]

Currently, two prospective randomized clinical trials (TAILORx and MINDACT) are addressing the use of OncotypeDx and MammaPrint, respectively, as predictive and/or prognostic tools in populations of women with early-stage, lymph node-negative breast cancer. Pending the results of the prospective trials, the Panel considers the 21-gene RT-PCR assay as an option when evaluating patients with primary tumors characterized as 0.6-1.0 cm with unfavorable features or >1 cm, and node-negative, hormone receptor-positive, and HER2-negative (category 2A [based on lower-level evidence and there is uniform consensus])."

• In 2009, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group reviewed the evidence for MammaPrint and concludes:4
  "It is unclear what population of patients would derive benefit from use of the test, and what the magnitude of that benefit would be. Prospective data from trials like MINDACT will be extremely valuable."
  "Overall, published evidence supports MammaPrint as a better predictor of the risk of distant recurrence than traditionally used tumor characteristics or algorithms, but its performance in therapeutically homogeneous populations is not yet known with precision, and it is unclear for how many women the lowest predicted risks are low enough to forgo chemotherapy."
  "No evidence is available to permit conclusions regarding the clinical utility of MammaPrint to select women who will benefit from chemotherapy."
  "To conclude, the literature on the 70-gene signature includes numerous studies that focused more on its biological underpinning and less on the clinical implications of this gene expression profile, although it has now received FDA approval for clinical use."

• Evidence-based clinical guidelines from the American Society of Clinical Oncology (2007) state that for multiparameter gene expression analysis for breast cancer:5
  "In newly diagnosed patients with node-negative, estrogen receptor-positive breast cancer, the Oncotype DX assay (Genomic Health Inc, Redwood City, CA) can be used to predict the risk of recurrence in patients treated with tamoxifen. Oncotype DX may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy."
  "The precise clinical utility and appropriate application for other multiparameter assays, such as the MammaPrint assay (Agendia BV, Amsterdam, the Netherlands), the so-called Rotterdam Signature, and the Breast Cancer Gene Expression Ratio are under investigation."

• The US Food and Drug Administration (FDA) cleared Mammaprint for clinical use in 2007.2

Criteria

Genetic testing is not approved for the MammaPrint multi-gene assay on tumor tissue because it is currently considered experimental, investigational or is unproven.
<table>
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<tr>
<th>NCD/LCD Jurisdiction and CPT Codes</th>
<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
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84999 CLINICAL CHEMISTRY TEST

MammaPrint

Yes

No

Yes

See LCD jurisdictions that refer to MolDX.

LCD: MolDX

[http://www.palmettobga.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Excluded%20Tests~8X6KG60461?open&navmenu=Browse*By*Topic]]

BluePrint

No

No

N/A

LCD: MolDX

[http://www.palmettobga.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Covered%20Tests~8SBH3U4732?open&navmenu=Browse%5EBy%5EETopic%7C%7C%7C%7C%7C]

References


Breast Cancer Prognosis (OncotypeDX Breast)

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<td>Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score</td>
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</table>

* - Clinical Review necessary prior to authorization for this procedure.† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Click here for applicable Medicare NCD/LCD information

What Is Oncotype DX?

- Oncotype DX® is a gene expression assay designed to determine the risk of a breast cancer recurrence within 10 years of the original diagnosis.¹
- It is intended for early stage, hormone receptor -positive, lymph node-negative breast cancer.¹⁻³
- Oncotype DX should be used with other standard methods of breast cancer assessment such as disease staging, grading, and other tumor markers.¹,²
- Oncotype DX results appear to correlate with chemotherapy benefit,⁴,⁵ which may help with the decision between tamoxifen only and adjuvant chemotherapy. Studies have demonstrated that the addition of Oncotype DX results changed treatment recommendations and decisions in 25% to 44% of patients, with the majority of recommendations changing from chemotherapy plus tamoxifen to tamoxifen only.⁶⁻⁸

Test Information

- Oncotype DX measures the expression level of 21 genes (16 cancer and 5 reference) from paraffin-embedded breast tumor tissue.¹ These sixteen genes consistently correlated with distant recurrence-free survival in three studies that explored the expression of 250 genes in breast tumor samples.⁴
- The results are provided as a Recurrence Score® (RS, 0-100) with higher scores reflecting higher risk of recurrence. Three risk categories help characterize prognosis:¹,²
  - Low risk (RS<18), ~50% of patients tested
    - Least aggressive tumors
    - Metastasis unlikely
    - 7% recurrence by 10 yrs
  - Intermediate risk (RS 18-30), ~25% of patients tested
    - More aggressive tumors
    - Metastasis more likely
    - 14% recurrence by 10 yrs
  - High risk (RS 31 or higher), ~25% of patients tested
- Most aggressive tumors
- Metastasis most likely
- 31% recurrence by 10 yrs

- Patients with high scores benefit the most from chemotherapy, showing a substantial reduction in 10 year recurrence. Patients with intermediate scores show questionable benefit from chemotherapy, whereas those with low scores benefit the least from chemotherapy.²⁴⁵

Guidelines and Evidence

- The National Comprehensive Cancer Network (NCCN) 2014 breast cancer treatment guidelines incorporate Oncotype DX Breast ("21-gene RT-PCR assay") in their treatment algorithm for hormone receptor-positive, HER2-negative breast cancer.⁹
  - They recommend considering the Oncotype DX assay in the following circumstances:
    - Histology: Ductal, Lobular, Mixed, Metaplastic
    - Tumor >0.5 cm (T1b-T3)
    - pN0 or pN1mi (<2mm axillary node metastasis)
  - In the discussion, NCCN guidelines state: "Pending the results of prospective trials, the Panel considers the 21-gene RT-PCR assay [Oncotype DX] as an option when evaluating patients with primary tumors characterized as 0.6-1.0cm with unfavorable features or >1cm, and node-negative, hormone receptor positive and HER2-negative (category 2A). In this circumstance, the recurrence score may be determined to assist in estimating likelihood of recurrence and benefit from chemotherapy."⁹ (Category 2B: The recommendation is based on lower level evidence and there is non-uniform NCCN consensus, but no major disagreement).

  - "Several tests are available which define prognosis. These may indicate a prognosis so good that the doctor and patient decide that chemotherapy is not required. A strong majority of the Panel agreed that the 21-gene signature (Oncotype DX) may also be used where available to predict chemotherapy responsiveness in an endocrine responsive cohort where uncertainty remains after consideration of other tests..."¹¹

- The Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP, 2009) found:
  - "Insufficient evidence to make a recommendation for or against the use of tumor gene expression profiles to improve outcomes in defined populations of women with breast cancer. For one test [Oncotype DX], the EWG found preliminary evidence of potential benefit of testing results to some women who face decisions about treatment options (reduced adverse events due to low risk women avoiding chemotherapy), but could not rule out the potential for harm for others (breast cancer recurrence that might have been prevented). The evidence is insufficient to assess the balance of benefits and harms of the proposed uses of the tests."¹²

- The 2007 evidence-based guidelines from the American Society of Clinical Oncology (ASCO) about breast cancer tumor marker use state:
  - "In newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer, the Oncotype DX assay can be used to predict the risk of recurrence in patients treated with tamoxifen. Oncotype DX may be used to identify patients who are predicted to obtain..."
the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy. In addition, patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically (C)MF) than from tamoxifen. There are insufficient data at present to comment on whether these conclusions generalize to hormonal therapies other than tamoxifen, or whether this assay applies to other chemotherapy regimens.3

- Additional clinical application issues:
  - **Male gender.** No studies specific to the application of Oncotype DX in men with breast cancer have been identified. In general, the NCCN breast cancer treatment guidelines do not differentiate treatment on the basis of gender9, which suggests Oncotype DX would not be excluded for males who meet NCCN clinical criteria for considering such testing.
  - **Multiple primary breast tumors.** No studies specific to the application of Oncotype DX in those with multiple breast primary cancers have been identified. Guidelines do not address this issue. A single poster summarized data in a study that used the Oncotype DX test to help assess if synchronous breast cancers were independent neoplastic events or spread of a single tumor. Of 11 patients who met criteria, 5 had different risk scores by Oncotype DX testing (with 3 of these patients having tumors assigned to different risk categories). Of these 5 with significantly different scores, 4 involved bilateral tumors and the other involved tumors in different quadrants. Comparing tumors by histology, 4 of 5 had clearly different histology and 1 had equivocal histology. Of the 6 with similar risk scores, 3 had the same histology, 2 equivocal, and in only 1 case was histology clearly different between the two tumors. This very limited data suggests OncotypeDX may be useful in multiple primaries when tumors independently meet criteria.
  - **Positive lymph nodes.** There is at least one clinical trial underway, RxPonder, to evaluate the utility of the Oncotype DX Breast Cancer assay for women with 1-3 positive lymph nodes (ER/PR-positive, HER2-negative).10 This trial aims to support chance findings from a retrospective subset analysis of the SWOG-8814 trial data that suggested Oncotype DX high and low risk scores were able to predict chemotherapy benefit regardless of node status. However, evidence to support use in node-positive disease remains limited and use in this population is controversial.9

**Criteria**

- **Testing Multiple Samples:**
  - No repeat Oncotype DX® testing on the same sample when a result was successfully obtained, and
  - When more than one breast cancer primary is diagnosed:
    - There should be reasonable evidence that the tumors are distinct (e.g., bilateral, different quadrants, different histopathologic features, etc.), and
    - There should be no evidence from either tumor that chemotherapy is indicated with or without knowledge of the Oncotype DX test result (e.g., histopathologic features or previous Oncotype DX result of one tumor suggest chemotherapy is indicated), and
    - If both tumors are to be tested, both tumors must independently meet the required clinical characteristics outlined below.

- **Required Clinical Characteristics:**
Invasive breast cancer meeting all of the following criteria:

- Tumor size >0.5cm (5mm) in greatest dimension (T1b-T3), and
- Estrogen receptor positive (ER+), and
- HER2 negative, and
- Patient has no regional lymph node metastasis (pN0) or only micrometastases (pN1mi, malignant cells in regional lymph node(s) not greater than 2.0mm), and
- Chemotherapy is a treatment option for the patient; results from this Oncotype DX test will be used in making chemotherapy treatment decisions, and

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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<th>Required ICD9 Codes?</th>
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84999 CLINICAL CHEMISTRY TEST

Oncotype DX breast cancer assay; Breast Cancer Gene Expression Ratio; MammaPrint; Rotterdam 76-Gene Signature; 41-gene signature assay; Amsterdam 70-Gene Profile

Yes Yes No

VA, NC, SC, WV

LCD: L33599

84999 CLINICAL CHEMISTRY TEST

Oncotype DX Breast

Yes No Yes

Oncotype DX Colon

Yes No Yes

See LCD jurisdictions that refer to MolDX.

 References

Brugada Syndrome (SCN5A Full Sequence and Deletion/Duplication analysis)

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<tr>
<td>Brugada syndrome gene analyses (SCN5A); duplication/deletion variants</td>
<td>81282</td>
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What Is Brugada Syndrome?

- Brugada syndrome (BrS) is an inherited channelopathy characterized by right precordial ST elevation. This can result in cardiac conduction delays at different levels, syncope and/or a lethal arrhythmia resulting in sudden cardiac death.
- Although the typical presentation of BrS is sudden death in a male in his 40s with a previous history of syncope, BrS has been seen in individuals between the ages of 2 days and 85 years1, as well as females.2
- The diagnosis of BrS is based on ECG results, clinical presentation and family history. A diagnosis of either type 1, 2 or 3 ECG results with a personal history of fainting spells, ventricular fibrillation, self-terminating polymorphic ventricular tachycardia, or electrophysiologic inducibility can help identify those at risk for BrS. A family history of syncope, coved-type ECGs, or sudden cardiac death, especially in an autosomal dominant inheritance pattern, can help aid in the diagnosis.3,4
- BrS has been associated with up to 13 different genes and >400 mutations3,5,6, and is estimated to be seen in about 1 in 2000 individuals. Approximately 65-75% of families with a clinical diagnosis of BrS do not test positive for a mutation in one of the known genes, suggesting that there are other genes that have not been identified.3,5
  - SCN5A is responsible for the majority of BrS cases (15-30%).
  - There are reports that CACNA1C and CACNB2B may account for up to 11% of cases of BrS.6,7
  - Each of the other genes comprise <5% of mutations in each case.
- BrS has variable expression and incomplete penetrance. Approximately 25% of gene positive individuals have an ECG diagnostic of BrS.3,5 Additionally, 80% individuals with a disease-causing mutation only present with symptoms when challenged with a sodium channel blocker.2,8
- BrS is found worldwide, but seems to have a higher incidence in Southeast Asia. In countries such as Japan, the Philippines, Laos, and Thailand, a condition called Sudden Unexplained Nocturnal Death syndrome (SUNDS) has been associated with mutations in the SCN5A, suggesting that this condition is actually Brugada Syndrome.9,10 In these countries, SUNDS is the second most common cause of death of men under age 40 years.3
- BrS is inherited in an autosomal dominant inheritance pattern. This means that an individual has a 50% chance of passing on a mutation to their children. Additionally, parents and siblings of known carriers have a 50% chance of being carriers of the same mutation. When a mutation in a child is
not found in the parents, it is assumed that there is a *de novo* mutation in the child. *De novo* mutations are estimated to occur in approximately 1% of cases. Siblings would still need to be tested to rule out germline mutations. A DNA test for BrS should be offered to the person who has the most obvious disease, as that individual will more likely test positive than someone without disease. At this time, population wide carrier screening for BrS is not recommended.

**Test Information**

- Full sequence analysis of the SCN5A gene is available through a number of commercial laboratories.
- Deletion/duplication testing for SCN5A is also available, and is typically done in reflex to a negative result from full sequence analysis.
- Testing will find a mutation in approximately 15-30% of individuals with clinical diagnosis of Brugada syndrome.

**Guidelines and Evidence**

- A 2011 expert consensus statement from the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) recommends:
  - “Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.”
  - “Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern.”
  - “Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.”

**Criteria**

**Brugada Syndrome Full Sequence Analysis of SCN5A**

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist, genetic counselor, or cardiologist, AND
- Previous Genetic Testing:
  - No previous genetic testing for Brugada Syndrome, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Type 1, 2, or 3 ECG results, and
  - Documented ventricular fibrillation, or
  - Self-terminating polymorphic ventricular tachycardia, or
  - A family history of sudden cardiac death, or
  - Coved-type ECGs in family members, or
  - Electrophysiologic inducibility, or
  - Syncope, or
o Nocturnal agonal respiration (breaths that persist after cessation of heartbeat), OR

- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  o Biologic relative(s) (1<sup>st</sup>, 2<sup>nd</sup>, or 3<sup>rd</sup> degree) diagnosed with BrS clinically, and no family mutation identified, or
  o Sudden death in biologic relative(1<sup>st</sup>, 2<sup>nd</sup>, or 3<sup>rd</sup> degree), and
  o Member (patient) has Type 1 ECG changes, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**Brugada Deletion/Duplication Analysis of SCN5A**

- Genetic Counseling
  o a. Pre and post-test counseling by a medical geneticist, genetic counselor, or cardiologist, AND
- Previous Genetic Testing:
  o No mutation identified with Brugada Syndrome sequence analysis of SCN5A, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**Medicare**

There are no NCDs or LCDs that specifically address Brugada Syndrome.

**References**

5. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace.* 2011;13(8):1077-1109.
Brugada Syndrome (Single Site Analysis)

<table>
<thead>
<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Requires:</th>
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<tr>
<td>Brugada syndrome gene analyses (eg, SCN5A); known familial sequence variant</td>
<td>Prior-authorization*</td>
<td>Yes</td>
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<td>Lab Procedure Restrictions †</td>
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</tbody>
</table>

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What Is Brugada Syndrome?

- Brugada syndrome (BrS) is an inherited channelopathy characterized by right precordial ST elevation. This can result in cardiac conduction delays at different levels, syncope and/or a lethal arrhythmia resulting in sudden cardiac death.
- Although the typical presentation of BrS is sudden death in a male in his 40s with a previous history of syncope, BrS has been seen in individuals between the ages of 2 days and 85 years, as well as females.
- The diagnosis of BrS is based on ECG results, clinical presentation and family history. A diagnosis of either type 1, 2 or 3 ECG results with a personal history of fainting spells, ventricular fibrillation, self-terminating polymorphic ventricular tachycardia, or electrophysiologic inducibility can help identify those at risk for BrS. A family history of syncope, coved-type ECGs, or sudden cardiac death, especially in an autosomal dominant inheritance pattern, can help aid in the diagnosis.
- BrS has been associated with up to 13 different genes and >400 mutations, and is estimated to be seen in about 1 in 2000 individuals. Approximately 65-75% of families with a clinical diagnosis of BrS do not test positive for a mutation in one of the known genes, suggesting that there are other genes that have not been identified.
  - SCN5A is responsible for the majority of BrS cases (15-30%).
  - There are reports that CACNA1C and CACNB2B may account for up to 11% of cases of BrS.
  - Each of the other genes comprise <5% of mutations in each case.
- BrS has variable expression and incomplete penetrance. Approximately 25% of gene positive individuals have an ECG diagnostic of BrS. Additionally, 80% individuals with a disease-causing mutation only present with symptoms when challenged with a sodium channel blocker.
- BrS is found worldwide, but seems to have a higher incidence in Southeast Asia. In countries such as Japan, the Philippines, Laos, and Thailand, a condition called Sudden Unexplained Nocturnal Death syndrome (SUNDS) has been associated with mutations in the SCN5A, suggesting that this condition is actually Brugada Syndrome. In these countries, SUNDS is the second most common cause of death of men under age 40 years.
- BrS is inherited in an autosomal dominant inheritance pattern. This means that an individual has a 50% chance of passing on a mutation to their children. Additionally, parents and siblings of known carriers have a 50% chance of being carriers of the same mutation. When a mutation in a child is not found in the parents, it is assumed that there is a de novo mutation in the child. De novo mutations are estimated to occur in approximately 1% of cases. Siblings would still need to be tested to rule out germline mutations. A DNA test for BrS should be offered to the person who has...
the most obvious disease, as that individual will more likely test positive than someone without disease. At this time, population wide carrier screening for BrS is not recommended.\(^5\)

**Test Information**

- Genetic confirmation of BrS can occur through sequence analysis and deletion analysis of the commonly affected genes. Testing typically begins in an individual in the family who has a clinical diagnosis of BrS. See the Brugada syndrome - DNA Analysis summary [NUMBER] for more information.
- Once a deleterious mutation is identified in a family member, at-risk relatives can be tested for only that specific mutation. Testing by single site analysis is greater than 99% accurate.\(^3\)

**Guidelines and Evidence**

- A 2011 expert consensus statement from the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) recommends:\(^5\)
  - “Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.”
  - “Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern.”
  - “Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.”

**Criteria**

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist, genetic counselor, or cardiologist, AND
- Previous Genetic Testing:
  - No previous genetic testing for Brugada Syndrome, AND
- Diagnostic and Predisposition Testing:
  - Brugada Syndrome family mutation identified in biologic relative(s), OR
- Prenatal Testing:
  - Brugada syndrome identified in biologic relative(s), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**References**


5. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace*. 2011;13(8):1077-1109.


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- BrS is inherited in an autosomal dominant inheritance pattern. This means that an individual has a 50% chance of passing on a mutation to their children. Additionally, parents and siblings of known carriers have a 50% chance of being carriers of the same mutation. When a mutation in a child is not found in the parents, it is assumed that there is a de novo mutation in the child. De novo mutations are estimated to occur in approximately 1% of cases. Siblings would still need to be tested to rule out germline mutations. A DNA test for BrS should be offered to the person who has the most obvious disease, as that individual will more likely test positive than someone without disease. At this time, population wide carrier screening for BrS is not recommended.
Test Information

- Commercial genetic testing is available for a number of genes shown to cause Brugada syndrome. The composition of multigene panels will vary by laboratory.
- Testing will find a mutation in approximately 24-41% of individuals with clinical diagnosis of Brugada syndrome.\textsuperscript{11,20}

Guidelines and Evidence

- A 2011 expert consensus statement from the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) recommends:\textsuperscript{5}
  - “Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.”
  - “Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern.”
  - “Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.”

Criteria

The clinical utility of Brugada multigene panels has not been well established. Mutations in SCN5A are responsible for 15-30% of cases of Brugada Syndrome, making it the most common known genetic cause of BrS. There are 7 other genes associated with BrS, but mutations in each gene account for <5% of cases of BrS, therefore mutation yield on a multi-gene panel is expected to be very low.\textsuperscript{5} For these reasons, Brugada multigene panels are not covered.

References


CADASIL (NOTCH3 Sequencing)

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<td>Prior-authorization* Yes Lab Procedure Restrictions† No</td>
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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

What Is CADASIL?

- CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is an adult-onset form of cerebrovascular disease. There are no generally accepted clinical diagnostic criteria for CADASIL and symptoms vary among affected individuals, however typical signs and symptoms include:1,2
  - Stroke-like episodes before age 60 years
  - Cognitive disturbance
  - Psychiatric/behavioral abnormalities
  - Migraine with aura
  - Recurrent seizures
- Brain Magnetic Resonance Imaging (MRI) findings include T2-signal-abnormalities in the white matter of the temporal pole and T2-signal-abnormalities in the external capsule.1-2
- CADASIL is a rare disease. Cases have been reported worldwide with a prevalence of 1 in 50,000 to 1 in 121,000 individuals, though this may be an underestimate.1-3
- CADASIL is thought to be the most common form of hereditary stroke and vascular dementia in adults.
- CADASIL is an autosomal dominant disease caused by mutations in the NOTCH3 gene. Each offspring of an individual with CADASIL has a 50% chance of inheriting the disease-causing mutation.
- To date, NOTCH3 is the only gene in which mutations are known to cause CADASIL. NOTCH3 encodes a transmembrane receptor that is primarily expressed in vascular smooth-muscle cells, preferentially in small arteries. Mutations in NOTCH3 generally increase or decrease the number of cysteine residues in the extracellular domain of the protein, which then accumulate in small arteries of affected individuals.1 These accumulations are seen as granular osmophilic material (GOM) deposits in the walls of affected vessels seen on biopsy and are a pathologic hallmark of CADASIL.1
- Management and treatment of individuals is generally symptomatic and supportive.1-3

Test Information

- CADASIL is suspected in an individual with the clinical signs and MRI findings as described above. A positive family history for stroke or dementia is also indicative of disease in symptomatic individuals. However, a negative family history should not exclude the diagnosis, as de novo mutations may occur.1,3
- In order to firmly establish a diagnosis of CADASIL, one or both of the following is required:
- Documentation of characteristic deposits within small blood vessels by skin biopsy.\textsuperscript{1-3}
  - Specificity of skin biopsy findings is high as the characteristic deposits have not been documented in any other disorder.\textsuperscript{3} Specificity has been reported to range from 45\%-100\%.\textsuperscript{3} Sensitivity and specificity can be maximized by to >90\% by immunostaining for NOTCH3 protein.
- Documentation of a typical NOTCH3 mutation by genetic gene sequencing.\textsuperscript{1-3}
  - Mutation detection may reach >95\% in individuals with strong clinical suspicion of CADASIL.\textsuperscript{1} To date, all mutations in \textit{NOTCH3} causing CADASIL have been in exons 2-24.\textsuperscript{1} Some laboratories outside of the US offer tiered testing beginning with sequence analysis of select exons followed by sequence analysis of the remaining exons if a mutation is not identified. Other laboratories offer only sequence analysis of the entire coding region. In the United States, a limited number of laboratories offer CADASIL testing and all perform full gene sequencing at the time of this review.
  - There is evidence of founder mutation in individuals from the islands of Taiwan and Jeju as well as Finland and middle Italy.\textsuperscript{3-5}

- A correct diagnosis of CADASIL is important because the clinical course of disease is different from individuals with other types of cerebral small-vessel disease and proven therapies for stroke have not been validated in individuals with CADASIL.\textsuperscript{3} However, no specific treatments for CADASIL exist.\textsuperscript{1-3}
- No clear genotype-phenotype correlations exist for individuals with CADASIL and symptoms can vary considerably even within families.\textsuperscript{3,4}
- Once a mutation in an affected individual has been identified, testing at risk individuals in the family is possible (see CADASIL- NOTCH3 Single Site Analysis test policy).

**Guidelines and Evidence**

- No evidence-based U.S. testing guidelines have been identified.
- Evidence from one 2009 retrospective cohort study suggests that an adequate skin biopsy for analysis of granular osmophilic material is a cost effective way to determine a diagnosis of CADASIL in symptomatic individuals.\textsuperscript{5} The authors suggest that biopsy results can be used to guide the decision for who should have genetic testing, particularly in individuals with no known familial mutation or from ethnic populations with no evidence of founder mutations.\textsuperscript{5}
- Patients with CADASIL should avoid anticoagulants, angiography, and smoking to avoid disease-related complications, so clinical utility is represented.\textsuperscript{1,3} Because of the risk for intracerebral hemorrhage, use of antiplatelets rather than anticoagulants is considered for prevention of ischemic attacks. Statins are used for treatment of hypercholesterolemia and antihypertensive drugs are used for hypertension.\textsuperscript{6}
- A two-center cohort study found that blood pressure and hemoglobin A1c levels were associated with cerebral mini bleeds in CADASIL patients.\textsuperscript{3} Therefore, controlling blood pressure and glucose levels may improve the clinical course of the disease. It is also reasonable to control for high cholesterol and high blood pressure given the high rate of ischemic stroke seen in CADASIL.\textsuperscript{3}
- Pescini et al (2012) published a scale to help guide clinicians in selecting patients for NOTCH3 genetic analysis due to a high probability of a CADASIL genetic diagnosis. This scale assigns weighted scores to common features of CADASIL. The authors state that their scale is “accurate
with optimal sensitivity and specificity values (96.7% and 74.2%, respectively); however, our results need to be confirmed and further validated.”

Criteria

- Genetic Counseling:
  - Pre and post-test counseling by a medical geneticist, genetic counselor, or other specialist as deemed by Health Plan policy, AND

- Previous Genetic Testing:
  - No previous genetic testing for NOTCH3 mutations, AND

- Diagnostic Testing:
  - Member has ambiguous or indeterminate results from both MRI and skin biopsy, and
  - A high index of suspicion remains for CADASIL diagnosis based on clinical findings, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

References


# CADASIL (NOTCH3 Single Site Analysis)

<table>
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## What Is CADASIL?

- CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is an adult-onset form of cerebrovascular disease. There are no generally accepted clinical diagnostic criteria for CADASIL and symptoms vary among affected individuals, however typical signs and symptoms include:\(^1,2\)
  - Stroke-like episodes before age 60 years
  - Cognitive disturbance
  - Psychiatric/behavioral abnormalities
  - Migraine with aura
  - Recurrent seizures
- Brain Magnetic Resonance Imaging (MRI) findings include T2-signal-abnormalities in the white matter of the temporal pole and T2-signal-abnormalities in the external capsule.\(^1,2\)
- CADASIL is a rare disease. Cases have been reported worldwide with a prevalence of 1 in 50,000 to 1 in 121,000 individuals, though this may be an underestimate.\(^1,3\)
- CADASIL is thought to be the most common form of hereditary stroke and vascular dementia in adults.
- CADASIL is an autosomal dominant disease caused by mutations in the NOTCH3 gene. Each offspring of an individual with CADASIL has a 50% chance of inheriting the disease-causing mutation.
- To date, NOTCH3 is the only gene in which mutations are known to cause CADASIL. NOTCH3 encodes a transmembane receptor that is primarily expressed in vascular smooth-muscle cells, preferentially in small arteries. Mutations in NOTCH3 generally increase or decrease the number of cysteine residues in the extracellular domain of the protein, which then accumulate in small arteries of affected individuals.\(^1\) These accumulations are seen as granular osmophilic material (GOM) deposits in the walls of affected vessels seen on biopsy and are a pathologic hallmark of CADASIL.\(^1\)
- Management and treatment of individuals is generally symptomatic and supportive.\(^1,3\)

## Test Information

- CADASIL is suspected in an individual with the clinical signs and MRI findings as described above. A positive family history for stroke or dementia is also indicative of disease in symptomatic individuals. However, a negative family history should not exclude the diagnosis, as de novo mutations may occur.\(^1,3\)
- In order to firmly establish a diagnosis of CADASIL, one or both of the following is required:
o Documentation of characteristic deposits within small blood vessels by skin biopsy.¹⁻³
  ▪ Specificity of skin biopsy findings is high as the characteristic deposits have not
    been documented in any other disorder.³ Specificity has been reported to range
    from 45%-100%.³ Sensitivity and specificity can be maximized by to >90% by
    immunostaining for NOTCH3 protein.

o Documentation of a typical NOTCH3 mutation by genetic gene sequencing.¹⁻³
  ▪ Mutation detection may reach >95% in individuals with strong clinical suspicion
    of CADASIL¹. To date, all mutations in NOTCH3 causing CADASIL have been in
    exons 2-24.¹ Some laboratories outside of the US offer tiered testing beginning
    with sequence analysis of select exons followed by sequence analysis of the
    remaining exons if a mutation is not identified. Other laboratories offer only
    sequence analysis of the entire coding region. In the United States, a limited
    number of laboratories offer CADASIL testing and all perform full gene sequencing
    at the time of this review.
    ▪ There is evidence of founder mutation in individuals from the islands of Taiwan
      and Jeju as well as Finland and middle Italy.³⁻⁵

  • A correct diagnosis of CADASIL is important because the clinical course of disease is different
    from individuals with other types of cerebral small-vessel disease and proven therapies for stroke
    have not been validated in individuals with CADASIL.³ However, no specific treatments for
    CADASIL exist.¹⁻³

  • No clear genotype-phenotype correlations exist for individuals with CADASIL and symptoms can
    vary considerably even within families.³,⁴

  • Once a mutation in an affected individual has been identified, testing at risk individuals in the family
    is possible (see CADASIL- NOTCH3 Single Site Analysis test policy).

Guidelines and Evidence

• No evidence-based U.S. testing guidelines have been identified.
• Evidence from one 2009 retrospective cohort study suggests that an adequate skin biopsy for
  analysis of granular osmophilic material is a cost effective way to determine a diagnosis of
  CADASIL in symptomatic individuals.⁵ The authors suggest that biopsy results can be used to
  guide the decision for who should have genetic testing, particularly in individuals with no known
  familial mutation or from ethnic populations with no evidence of founder mutations.⁵
• Patients with CADASIL should avoid anticoagulants, angiography, and smoking to avoid disease-
  related complications, so clinical utility is represented.¹,³ Because of the risk for intracerebral
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  ischemic attacks. Statins are used for treatment of hypercholesterolemia and antihypertensive
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  weighted scores to common features of CADASIL. The authors state that their scale is “accurate
with optimal sensitivity and specificity values (96.7% and 74.2%, respectively); however, our results need to be confirmed and further validated.”

Criteria

- Genetic Counseling:
  - Pre and post-test counseling by a medical geneticist, genetic counselor, or other specialist as deemed by Health Plan policy, AND
- Previous Genetic Testing:
  - No previous genetic testing for NOTCH3 mutations, AND
- Predictive Testing:
  - Member has a first-degree relative (i.e. parent, sibling, child) with an identified NOTCH3 gene mutation, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

References

Canavan Disease

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<tr>
<th>Procedure(s) covered by this policy:</th>
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<th>Lab Procedure Restrictions†</th>
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<td>ASPA targeted mutation analysis for common mutations</td>
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<td>ASPA full sequencing analysis</td>
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Click here for applicable Medicare NCD/LCD information

Description

Canavan disease (CD) is an autosomal recessive condition caused by mutations in the ASPA gene, which encodes the aspartoacylase enzyme. CD is characterized by a large head size (macrocephaly), lack of head control, developmental delay (usually by three to five months), and severe low muscle tone (hypotonia). Individuals with Canavan disease are unable to sit by themselves, walk or speak. Optic atrophy is a common finding in CD; however, the children are not blind and can track objects. Hearing is not usually impaired. The triad of hypotonia, macrocephaly and head lag in an infant after the age of three to five months should raise the suspicion of CD. While three forms of CD have been reported (neonatal, infantile and late onset), the infantile form of the disease tends to be the norm; however, the rate of progression can be highly variable and over time, hypotonia gives way to spasticity. The life expectancy of individuals with Canavan disease is reduced; depending on the clinical course and the medical care provided, the life expectancy can be anywhere from the first few years of life, into the teens and beyond.

CD is inherited in an autosomal recessive inheritance pattern. Therefore individuals usually do not have other affected family members. However, the parents of an affected individual are obligate carriers; siblings have a 50% chance of being carriers of the condition, and a 25% chance of being affected. Carriers of CD are asymptomatic and do not exhibit any features of the condition. Mutations in ASPA are found in all ethnic groups, but most commonly seen in the Ashkenazi Jewish population. The carrier rate in the non-Jewish population is unknown; however, the carrier rate in the Ashkenazi Jewish population is approximately 1 in 40. In this population, there are two common mutations that are seen in approximately 97% of carriers. Based on this carrier rate, the prevalence of affected individuals in the Ashkenazi Jewish population is approximately one in 6400.

Diagnosis of CD occurs through measuring N-acetylaspartic acid (NAA) in urine, blood or amniotic fluid, measuring aspartoacylase enzyme activity in skin cells, white blood cells or amniocytes/CVS, or molecular genetic testing. Elevated levels of NAA, the absence of aspartoacylase enzyme activity or a mutation in the ASPA gene are all diagnostic for CD. While biochemical testing can be used to confirm a diagnosis of CD in an individual who is symptomatic, it cannot be used to test for carrier status of an at-risk relative. When molecular testing is performed to confirm a diagnosis in an individual who is showing symptoms, other family members can then be screened for those mutations. Once a deleterious mutation has been identified, relatives of affected individuals can be tested. Individuals who are at risk for having a child with
CD can have prenatal testing of their fetus. Prenatal testing is available and is can be performed through biochemical testing, or mutation analysis if both parental mutations are known.\(^2\)

Preventive use of genetic testing on a population wide basis, for any condition, may be cost-effective if genotypic information can be shown to predict disease risk. Population-wide screening is ethically justifiable only if there is an efficacious and cost-effective intervention to prevent the disorder in those who are identified as being at increased risk. Therefore, population wide carrier screening for Canavan Disease is not recommended unless an individual is of Ashkenazi Jewish descent.\(^3\) Targeted mutation analysis of \(\text{ASPA}\) is available as a single multiplex assay for individuals of Ashkenazi Jewish descent. The Ashkenazi Jewish panel targets mutations associated with several autosomal recessive conditions with increased prevalence in this population. This can be practical from a convenience and cost perspective. However, an individual should be consented for each condition in the panel. If an individual does not consent to being tested for a particular condition, then each test should be ordered individually.\(^3,6\) Please see the Ashkenazi Jewish Screening Panel policy for more information.

The American College of Medical Genetics (ACMG) supports offering carrier testing for CD to individuals of Ashkenazi Jewish descent for the two common mutations. It is anticipated that the detection rate will be \(~97\%\). This test should be offered to individuals of reproductive age, preferentially prior to pregnancy, with genetic counseling performed by a geneticist or genetic counselor. Counseling should include the following: 1) a description of the condition, 2) discussion of carrier risk associated with a negative test result, 3) the risk of passing the gene onto future offspring, and 4) discussion of the implications of a positive test on other family members. ACMG supports the testing of individuals of Ashkenazi Jewish descent, even when their partner is non-Ashkenazi Jewish. In this situation, testing would start with the individual who is Ashkenazi and reflex back to the partner if necessary.\(^3\)

The American College of Obstetrics and Gynecologists (ACOG) recommends that individuals who are considering a pregnancy or are pregnant should consider testing if at least one member of the couple is Ashkenazi Jewish or has a relative with CD. If the woman is pregnant, testing may need to be conducted on both partners simultaneously in order to receive results in a timely fashion. If one or both partners are found to be carriers of CD, genetic counseling should be provided, and prenatal testing offered, if appropriate.

As a result of the above guidelines, it is determined that genetic testing should be approved to confirm a diagnosis in anyone who meets clinical criteria for CD. Additionally, genetic testing should be approved to determine carrier status in an at risk relative with a known genetic mutation. Individuals who have a family member with a known CD mutation(s) should be tested for that/those mutation(s). Individuals who meet clinical criteria for CD should be offered sequence analysis. Finally, individuals of Ashkenazi Jewish descent should be offered carrier testing of the common mutations in this population. If they test negative, and do not meet any other criteria for genetic testing, they should not continue on to sequence analysis.

**Criteria**

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

**Known \(\text{ASPA}\) Family Mutation Testing**

- Genetic Counseling:
Canavan Disease

- Pre and post-test counseling by a medical geneticist or genetic counselor, AND
- Previous Genetic Testing:
  - No previous genetic testing of ASPA, AND
- Carrier Screening for Asymptomatic Individuals:
  - Known family mutation in ASPA in 1st, 2nd, or 3rd degree biologic relative, OR
- Prenatal Testing for At-Risk Pregnancies:
  - ASPA mutations identified in both biologic parents

ASPA Targeted Mutation Analysis for Common Mutations

Note: Ashkenazi Jewish individuals are recommended to have the full AJ Panel regardless of symptoms of disease. See Ashkenazi Jewish Disease Carrier Screening policy.

- Genetic Counseling:
  - Pre and post-test counseling by a medical geneticist or genetic counselor, AND
- Previous Genetic Testing:
  - No previous ASPA genetic testing, including AJ screening panels containing targeted mutation analysis for Canavan disease, AND
- Diagnostic Testing or Carrier Screening:
  - Ashkenazi Jewish descent, regardless of disease status and N-acetylaspartic acid (NAA) levels, OR
- Prenatal Testing for At-Risk Pregnancies:
  - ASPA Ashkenazi mutations identified in both biologic parents.

ASPA Full Sequence Analysis†

- Genetic Counseling:
  - Pre and post-test counseling by a medical geneticist or genetic counselor, AND
- Previous Genetic Testing:
  - No previous ASPA gene sequencing and
  - No known ASPA mutation in family, and
  - No mutations or one mutation detected by common mutation panel, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Increased levels of N-acetylaspartic acid (NAA) in urine, and
  - An individual age three to five months of age with a triad of hypotonia, macrocephaly and head lag, or
  - Failure to attain independent sitting, walking or speech, OR
- Testing for Individuals with Family History or Partners of Carriers:
  - 1st, 2nd, or 3rd degree biologic relative with Canavan disease clinical diagnosis, family mutation unknown, and testing unavailable, or
  - Partner is monoallelic or biallelic for ASPA mutation, and
    - Have the potential and intention to reproduce

†Lab Testing Restrictions: Full Sequence Analysis is authorized if no known ASPA mutation in family, or no mutations or one mutation detected by common mutation panel.
**Canavan Disease**

### CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV


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<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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</thead>
<tbody>
<tr>
<td>No</td>
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81200 ASPA GENE

### FL, PR, VI


<table>
<thead>
<tr>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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<tr>
<td>No</td>
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81200 ASPA GENE

### VA, NC, SC, WV


<table>
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<th>Test-Specific Criteria?</th>
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<tbody>
<tr>
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81200 ASPA GENE

See LCD jurisdictions that refer to MolDX.


<table>
<thead>
<tr>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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<tbody>
<tr>
<td>No</td>
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81200 ASPA GENE

### References


Cancer of Unknown Primary

<table>
<thead>
<tr>
<th>Procedure(s) covered by this policy</th>
<th>Procedure Code(s)</th>
<th>Requires:</th>
<th>Non-covered</th>
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<tbody>
<tr>
<td>Unlisted molecular pathology procedure</td>
<td>81479</td>
<td>Yes</td>
<td>Investigational and Experimental</td>
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<tr>
<td>Unlisted chemistry procedure</td>
<td>84999</td>
<td>Yes</td>
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</tr>
<tr>
<td>Cancer of Unknown Primary Testing</td>
<td>81504</td>
<td>Yes</td>
<td>Investigational and Experimental</td>
</tr>
</tbody>
</table>

* - Clinical Review necessary prior to authorization for this procedure.

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What Is Cancer of Unknown Primary Testing?

In order to determine the most effective treatment regimen for a patient with cancer it is important to identify the cancer cell type.1

- When a cancer is found in one or more metastatic sites but the primary site is not known, it is called a cancer of unknown primary (CUP).2 This happens in a small portion of cancers.
- The most commonly used techniques to identify tissue of origin (TOO) for CUP include light microscopy, immunohistochemistry (IHC) staining and computed tomography (CT) or positron emission tomography (PET) imaging.1
- With advances in technology, some laboratory tests utilize gene expression profiling or other molecular techniques in cancer cells. Ramaswamy et al. found that a gene expression signature distinguished primary from metastatic adenocarcinomas.3 By comparing the pattern of gene expression in the CUP sample to the patterns seen with other known types of cancer, a CUP may be identified as belonging to a particular cancer type.

Test Information

- A number of different companies and approaches are being utilized to diagnose metastatic neoplasms for patients with CUP. These include but are not limited to:
  - ResponseDX Tissue of Origin Test- uses microarray analysis to measure the expression of over two thousand genes.4
  - CancerType ID from Biotheranostics analyzes the expression of 92 genes.5
  - Cancer Origin Test from Rosetta Genomics- uses a RT-PCR platform to analyze the expression levels of 64 microRNAs (miRNAs).6

Guidelines/Evidence

- Under 2014 NCCN guidelines for CUP (occult primary), gene signature profiling for tissue of origin is not recommended for standard management at this time. The panel states that “there may be diagnostic benefit, not necessarily clinical benefit” and characterizes the use of gene signature
profiling for CUP as a category 3 recommendation. The panel also states that “until more robust outcomes and comparative effectiveness data are available, pathologists and oncologists must collaborate on the judicious use of these modalities on a case by case basis.”

- In a systematic review of cancer of unknown primary site in Lancet, gene-profiling diagnosis was noted to have high sensitivity, but additional prospective studies were deemed necessary to establish whether patients’ outcomes are improved by its clinical use.

Criteria

Genetic testing is not approved for Cancer of Unknown Primary testing because it is currently considered experimental, investigational or unproven.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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<tr>
<td>81479</td>
<td>Rosetta Cancer Origin Test</td>
<td>Yes</td>
<td>No</td>
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</tbody>
</table>

See LCD jurisdictions that refer to MolDX.

- LCD: MolDX
  - 84999 UNLISTED CHEMISTRY PROCEDURE, ResponseDX Tissue of Origin Test, Available at: http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Covered%20Tests~8TQRBP1713?open&navmenu=Browse%5eBy%5eTopic[|||
  - 84999 UNLISTED CHEMISTRY PROCEDURE, bioTheranostics Cancer TYPE ID, Available at: http://www.biotheranostics.com

References

5. CancerTYPE ID. Biotheranostics Website. Available at: http://www.biotheranostics.com
## Carrier Status for Multiple Diseases (Multiplex Carrier Screening)

<table>
<thead>
<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Requires:</th>
<th>Lab Procedure Restrictions†</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Procedure Code(s)</td>
<td>Prior-authorization*</td>
</tr>
<tr>
<td><strong>CFTR</strong> (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)</td>
<td>81220</td>
<td>No</td>
</tr>
<tr>
<td><strong>CFTR</strong> (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence</td>
<td>81223</td>
<td>Yes</td>
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<tr>
<td><strong>SMN1</strong> (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy), exon 7 deletion Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)</td>
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<td>No</td>
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<tr>
<td><strong>SMN1/SMN2</strong> (survival of motor neuron 1, telomeric/survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy), dosage analysis (eg, carrier testing)] Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)</td>
<td>81401</td>
<td>Yes</td>
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<tr>
<td><strong>FMR1</strong> (Fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles</td>
<td>81243</td>
<td>No</td>
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<tr>
<td><strong>HBA1/HBA2</strong> (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydropsfetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)</td>
<td>81257</td>
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<tr>
<td><strong>HBB</strong> (hemoglobin, beta, beta-globin) (eg, beta thalassemia), duplication/deletion analysis Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using</td>
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</table>
### Multiplex Carrier Screening

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Code</th>
<th>Coverge</th>
<th>Formulary</th>
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<tbody>
<tr>
<td>Multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons</td>
<td>81404</td>
<td>No</td>
<td>No</td>
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<tr>
<td><strong>HBA1/HBA2</strong> (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia), duplication/deletion analysis</td>
<td>81404</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)</td>
<td>81404</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Hemoglobin fractionation and quantitation; electrophoresis (eg. A2, S, C and/or F)</td>
<td>83020</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>ASPA</strong> (aspartoacylase) (eg, Canavandisease) gene analysis, common variants (eg, E285A, Y231X)</td>
<td>81200</td>
<td>No</td>
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<tr>
<td><strong>BCKDHB</strong> (branched-chain keto acid dehydrogenase E1,beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)</td>
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<td><strong>BLM</strong> (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant</td>
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<td><strong>FANCC</strong> (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A&gt;T)</td>
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<td>No</td>
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<tr>
<td><strong>G6PC</strong> (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)</td>
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<td><strong>GBA</strong> (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G&gt;A)</td>
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<td><strong>HEXA</strong> (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G&gt;C, G269S)</td>
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<tr>
<td><strong>IKBKAP</strong> (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T&gt;C, R696P)</td>
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<tr>
<td><strong>MCOLN1</strong> (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-</td>
<td>81290</td>
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</table>
**What Is Multiplex Carrier Screening?**

- Multiplex carrier screening tests are designed to identify carrier status or predict risk for many genetic diseases (70 or more) in a single test. It is typically offered to patients planning a pregnancy or currently pregnant. The genetic diseases that are tested for range in severity from lethal in infancy to so mild an affected individual may never develop symptoms. Some conditions are quite common, especially in certain ethnic groups, while others are rare.
- A carrier has a single recessive gene mutation that does not cause symptoms for the person with the mutation. Most commonly, both parents have to be carriers of the same genetic condition to...
have an affected child. In this case, each pregnancy has a 25% risk to be affected when both parents are carriers of mutations in the same gene.

- Multiplex panel genetic screening tests may include mutations for some X-linked conditions as well. In this case, a mother can be an unaffected carrier but is at risk to have a son with the genetic disease if she passes on that mutation. The father does not need to be a carrier to have an affected child in this situation.
- It is generally believed that all people carry several recessive gene mutations. An estimated 1 in 580 births has an autosomal recessive condition and 1 in 2000 have an X-linked condition.\(^1\)
- Carrier screening is most commonly done for reproductive planning, to identify couples at risk for having a child with a recessive inherited disorder. Carrier screening for a specific disorder may be done when there is a positive family history, in adult adoptees with limited family history, and for couples who are consanguineous.

**Test Information**

- Several multiplex carrier screening tests are available. Each test has a unique set of diseases included in novel and proprietary genetic testing platforms. The number of mutations tested varies considerably by condition, ranging from a single mutation for rare conditions to over 100 mutations for cystic fibrosis.
- Complete testing information, including a list of all conditions screened, can be found at the laboratory websites. Examples of multiplex carrier screening tests include:
  - Carrier Status DNA Insight (Pathway Genomics)
  - Counsyl Universal Carrier Screening
  - Good Start
  - Inherigen (GenPath)
  - InheriTest Carrier Screen (Integrated Genetics)
  - Natera One
  - nxtPanel (Progenity)

**Guidelines and Evidence**

- No evidence-based guidelines have addressed simultaneous carrier screening for a large number of disorders.
- The American College of Medical Genetics and Genomics (ACMG; 2013) published a position statement on prenatal/preconception carrier screening. This statement did not provide evidence-based guidance for specific tests or conditions. Rather, it provides general considerations for disease inclusion, clinical relevance, laboratory performance, reporting, and genetic counseling.\(^2\)
- Current guidelines from the American College of Obstetrics and Gynecology (ACOG) and/or the American College of Medical Genetics (ACMG) only address 12 of the genetic conditions included in available multiplex carrier screening tests: \(^3-8\)
  - Ashkenazi Jewish Genetic Diseases: \(^6\)
    - Bloom syndrome
    - Canavan disease
    - Cystic fibrosis
    - Familial dysautonomia
    - Fanconi anemia type C
### Multiplex Carrier Screening

- Gaucher disease
- Mucolipidosis IV
- Niemann-Pick disease type A
- Tay-Sachs disease
  - Beta-thalassemia
  - Cystic fibrosis
  - Sickle cell disease
  - Spinal muscular atrophy

Although such large panels are usually significantly less expensive than doing each carrier screening test individually, most of the included tests are rarely indicated for such reasons as:

- Mutation analysis is not the preferred initial screening test for some. For example, a CBC with RBC indices is the initial screening test for beta-thalassemia followed by hemoglobin analysis for individuals with microcytic anemia.\(^3\) Measuring hexosaminidase A activity may be preferable to mutation analysis for Tay-Sachs carrier screening, especially in non-Jewish populations.\(^4\)
- Depending on ethnicity, currently multiplex screening panels are expected to identify up to 40% of people tested as carriers of a recessive gene mutation. Therefore, if this screening is routinely offered, many patients will require counseling for a positive result, and partner testing must be offered. The most complete partner testing is often by full gene sequencing. Availability of partner testing, cost, turnaround time, and the possibility of identifying a variant of unknown significance by sequencing make this a complex clinical scenario to manage in the routine reproductive setting.
- Some conditions included in multiplex carrier screens are exceedingly rare except in certain ethnicities.
- Some multiplex carrier screens include testing for conditions that are relatively mild, treatable, or have onset in adulthood.
- The remaining tests included in multiplex carrier screens have not been recommended for population-based carrier screening.

### Criteria

Individual gene(s) included in multiplex carrier screening panels should be covered based on the medical necessity criteria for each. Any genes that are included in a multiplex panel but do NOT meet medical necessity criteria are not a covered service. It will be at the laboratory, provider, and patient’s discretion to determine if a multi-gene panel remains the preferred testing option. See the gene-specific policies for guidance:

- Alpha-1 Antitrypsin Deficiency
- Alpha-Thalassemia
- Ashkenazi Jewish Diseases
  - Bloom Syndrome
  - Canavan Disease
  - Familial Dysautonomia
  - Familial Hyperinsulinism
  - Fanconi Anemia
  - Gaucher Disease
  - Glycogen Storage Disease Ia
- Maple Syrup Urine Disease
- Mucolipidosis IV
- Nemaline Myopathy
- Niemann Pick Disease, Types A and B
- Tay-Sachs Disease
- Usher Syndrome, Type III

- Beta-Thalassemia
- Cystic Fibrosis
- Fragile X Syndrome
- Sickle Cell Disease
- Spinal Muscular Atrophy
- Tay-Sachs Disease

For tests without a specific policy, use the Genetic Testing for Carrier Status Policy.

References

CCR5 Tropism Testing

<table>
<thead>
<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Requires:</th>
<th>Procedure Code(s)</th>
<th>Lab Procedure Restrictions†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR5 tropism testing for maraviroc (Selzentry®) response for HIV treatment</td>
<td>Prior-authorization*</td>
<td>81400</td>
<td>No</td>
</tr>
</tbody>
</table>

* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Description

Maraviroc (Selzentry®) is a drug used in combination with other antiretroviral drugs for the treatment of human immunodeficiency virus type 1 (HIV-1). This drug inhibits the ability of HIV-1 to bind to the CCR5 receptor on infected T-cells. It is indicated for use in individuals infected only with CCR5-tropic HIV-1. According to current FDA labeling, CCR5 tropism testing should guide treatment with maraviroc. HIV-1 treatment guidelines state that the CCR5 tropism assay should be performed whenever the use of a CCR5 inhibitor is being considered and when an individual exhibits virologic failure on a CCR5 inhibitor.

Criteria

CCR5 tropism testing is indicated in individuals with HIV-1 considering maraviroc therapy or taking a CCR5 inhibitor with evidence of failure therapy.

References

Celiac Disease

### Procedure(s) covered by this policy:

<table>
<thead>
<tr>
<th>Procedure(s)</th>
<th>Requires:</th>
<th>Lab Procedure Restrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA Class II typing, low resolution (e.g., antigen equivalents); 1 antigen equivalent. [Note: This code addresses several HLA allele tests and is not specific to celiac-associated HLA variants.]</td>
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<td>No</td>
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<tr>
<td>HLA Class II typing, high resolution (i.e., alleles or allele groups); 1 locus (e.g., HLA-DRB1, -DRB3, -DRB4, -DRB5, -DQB1, -DQA1, -DPB1, or -DPA1). [Note: This code addresses several HLA allele tests and is not specific to celiac-associated HLA variants.]</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HLA Class II typing, high resolution (i.e., alleles or allele groups); 1 allele or allele group (e.g., HLA-DQB1*0602). [Note: This code addresses several HLA allele tests and is not specific to celiac-associated HLA variants.]</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

### Description

- Celiac disease is an immune-mediated disorder that mainly affects the digestive tract.\(^1\text{-}^4\)
- Symptoms include diarrhea, constipation, vomiting, abdominal pain and bloating, growth problems, iron deficiency anemia, osteoporosis and other complications of malabsorption.\(^1\text{-}^4\)
- Celiac disease affects infants, children, and adults and can present at any age. It affects about 1 in every 100 people in the U.S.\(^2\text{-}^3\)
- Celiac is caused by exposure to dietary gluten (a protein molecule found in wheat, barley and rye) in people who are predisposed based on their genetic makeup.\(^1\text{-}^4\)
- Patients with certain medical conditions and relatives of people with celiac disease are known to have an increased risk of developing the condition.\(^2\text{-}^3\)
- An initial diagnosis of celiac disease is highly suspected based on serologic testing and is confirmed by finding characteristic changes on intestinal biopsy. Intestinal biopsy remains the gold standard for making a diagnosis of celiac disease.\(^1\text{-}^4\)
- Two genetic markers are associated with celiac disease — HLA-DQ2 and HLA-DQ8. These variants are present in about 30-40% of the general population, but more than 99% of patients with celiac disease have one or more of these variants.\(^1\) If a person suspected of having celiac disease is found not to have one of these markers, the diagnosis can be essentially excluded.\(^2\text{-}^4\)
- Consensus-based guidelines from the American Gastroenterological Association (2006)\(^2\), the National Institutes of Health (2005)\(^3\) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (2005)\(^4\) support the use of testing as follows.
  - HLA typing for celiac disease is appropriate for ruling out celiac disease in people who:
    - Have ambiguous or indeterminate results from serology and biopsy\(^2\text{-}^4\)
• Started a gluten-free diet without appropriate diagnostic testing and refuse or are unable to undergo a gluten challenge\textsuperscript{2,3}
• Have an increased risk for celiac disease because of their family or medical history\textsuperscript{2,4}

- There is strong evidence supporting the role of HLA typing for \textbf{excluding a diagnosis} of celiac disease in symptomatic and at-risk patients who have negative test results. However, positive test results cannot confirm a diagnosis, because the HLA-DQ2 and -DQ8 markers are very common in the general population.\textsuperscript{1-4}

\section*{Criteria}

Consideration for genetic testing for celiac-associated HLA variants DQ2 and DQ8 is determined according to diagnostic guidelines from the American Gastroenterological Association, NIH Consensus Development Conference Statement on Celiac Disease, and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.\textsuperscript{2,4}

Testing may be considered in individuals who meet the following criterion:
- Celiac disease is in the differential diagnosis, but the individual has had ambiguous or indeterminate results from serology and biopsy

\section*{References}

Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood): 86152

Physician interpretation and report, when required: 86153

**Description**

Circulating tumor cells (CTC) are tumor cells that have detached from the primary tumor site and entered the bloodstream. CTCs play a critical role in the metastasis of cancer. Several clinical studies have found that identifying CTCs can predict survival and are an important prognostic factor.

CellSearch™ is an FDA-approved CTC detection technique. Clinical trials have shown that CellSearch™ is an independent predictor of progression-free survival and overall survival in metastatic breast, prostate, and colon cancer. However, the American Society of Clinical Oncology (ASCO) does not recommend CellSearch™ because clinical utility data are limited.

**Criteria**

CellSearch™ is considered investigational at this time and is not routinely indicated.

**References**

**Charcot-Marie-Tooth (CMT)**

<table>
<thead>
<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Procedure Code(s)</th>
<th>Requires:</th>
<th>Prior-authorization*</th>
<th>Lab Procedure Restrictions†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known PMP22 Family MutationTesting</td>
<td>81326</td>
<td>No</td>
<td>No</td>
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<tr>
<td>PMP22 (peripheral myelin protein 22)</td>
<td>81324</td>
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<td>No</td>
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<tr>
<td>gene duplication/deletion analysis</td>
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<td>PMP22 full gene sequence analysis</td>
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<td>Molecular pathology procedure, Level 4, GJB1 full sequence analysis</td>
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<td>Molecular pathology procedure, Level 5, EGR2 full gene sequence analysis</td>
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<td>Molecular pathology procedure, Level 5, LITAF full gene sequence analysis</td>
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<td>Molecular pathology procedure, Level 6, MPZ full gene sequence</td>
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<td>Molecular pathology procedure, Level 6, NEFL full gene sequence</td>
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<tr>
<td>Unlisted molecular pathology procedure, (eg, MFN2, GDAP1, GARS, RAB7, HSPB1, and other CMT-associated genes)</td>
<td>81479</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>CMT Advanced Evaluation- Comprehensive (Athena Diagnostics)</td>
<td>81324</td>
<td>Non-covered</td>
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</table>

* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specific sequence to be followed or additional information is required and must be supplied by the lab performing procedure(s) for full claim payment.

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**Description**

Charcot-Marie-Tooth (CMT), also known as hereditary motor and sensory neuropathy (HMSN), refers to a group of peripheral nerve disorders that are characterized by distal muscle weakness, distal muscle atrophy, mild to moderate sensory loss, depressed tendon reflexes and high-arched feet. The prevalence of CMT is approximately 1:3300. Over 40 different genes/loci have been reported to cause CMT.¹

CMT1 is the most common form of CMT, accounting for approximately 40-50% of all CMT. CMT1 is an autosomal dominant demyelinating peripheral neuropathy. There are 6 subtypes of CMT1 that are distinguished by molecular characteristics alone, as the clinical presentation is similar in all types. CMT1A
is the most common subtype of CMT1, accounting for 70-80% of CMT1. Clinical presentation is variable and usually slowly progressive. Symptoms include distal muscle weakness and atrophy, pes cavus, bilateral foot drop, and slow nerve conduction velocity (5-30m/sec). Affected individuals can show symptoms starting from 5-25 years of age, with the an earlier onset for more severe forms. In more than 90% of individuals with CMT1, a mutation is found in the PMP22, MPZ, or GJB1 gene.1 2

CMT2 is an axonal (non-demyelinating) peripheral neuropathy that is clinically similar to CMT1. However, clinical symptoms are often less significant, with affected individuals having less sensory loss and less significant disability. Nerve conduction velocities are most often in the normal range. CMT2 accounts for 10-15% of all cases of CMT. There are 17 subtypes of CMT2, with CMT2A2 reported to be the most common type, accounting for 20% of CMT2. CMT2 is most often inherited in an autosomal dominant pattern, but a few subtypes of CMT2 are inherited in an autosomal recessive pattern.1

CMT4 can be distinguished from the other forms of demyelinating and axonal CMT based on its autosomal recessive inheritance pattern. The autosomal recessive forms of CMT are rare; CMT4 accounts for less than 10% of all CMT and is most often associated with early onset and greater severity of symptoms.4 Clinical symptoms are consistent with CMT1, including foot drop, sensory loss, pes cavus, distal muscle weakness and atrophy. Nerve conduction velocities are usually slow (less than 40 m/sec). There are 9 subtypes of CMT4, but the proportion of CMT4 attributed to each type is unknown.1

X-Linked CMT can be distinguished from other forms of CMT by the lack of male to male transmission in a family. Affected males typically have moderate to severe sensory motor neuropathy. CNS symptoms and sensorineural deafness have also been reported in some families with X-linked CMT. Carrier females are most often unaffected, but may have mild symptoms. Five types of X-linked CMT have been described, with CMTX1 accounting for 90% of cases.1

Guidelines and Evidence
American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of laboratory and genetic testing (an evidence based review).3

These guidelines recommend genetic testing that is “guided by the clinical phenotype, inheritance pattern (if available), and electrodiagnostic features (demyelinating and axonal).” The AAN recommends that genetic testing is focused on the most common genes, including PMP22, GJB1, and MPZ, which account for 90% of CMT mutations. The AAN does not support complete panels of all known CMT genes, but rather recommends a stepwise evaluation method to improve genetic screening efficiency.3

Given the above guidelines, small panels of testing based on inheritance pattern or electrodiagnostic features may be appropriate, but complete panels of all known CMT genes are not covered.

Criteria
Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.
Known Family CMT Mutation(s) Testing

- Genetic Counseling:
  - Pre and post-test counseling by a medical geneticist, genetic counselor, or other specialist as deemed by Health Plan policy, AND
- Previous Genetic Testing:
  - No previous genetic testing for known CMT family mutations, AND
- Diagnostic or Predisposition Testing and Carrier Screening:
  - ≥ 1 blood relative (1st, 2nd, or 3rd degree) with confirmed CMT mutation identified by molecular or genetic testing, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CMT1 and CMTX Testing†

Rationale: Individuals with inherited CMT phenotypes CMT1 and CMTX, which are characterized by variable degrees of demyelinating peripheral neuropathy, comprise 60-70% of the population with CMT. In more than 90% of individuals with CMT1 (demyelinating) phenotypes a mutation is found in one of the three genes (PMP22 duplication, MPZ, GJB1). The AAN recommends a tiered approach to testing for causative gene mutations.

- Genetic Counseling:
  - Pre and post-test counseling by a medical geneticist, genetic counselor, or other specialist as deemed by Health Plan policy, AND
- Previous Genetic Testing:
  - No previous genetic testing for the mutation(s) requested, and
  - No known family mutation, AND
- Diagnostic Testing of Symptomatic Individuals:
  - Standard neurological & physical exam excludes other causes of neuropathy, and
  - Abnormal NCV studies, and
  - Progressive weakness in the distal muscles of feet and/or hands, or
  - Abnormal EMG studies suggestive of CMT, or
  - Sural nerve biopsy indicates that diagnosis is CMT of demyelinating type, and
  - Clinical diagnosis or suspected diagnosis of CMT Type 1 or type CMT type X, OR
- Predisposition Testing or Carrier Screening:
  - Clinical diagnoses of CMT1 or CMTX in two generations (1st or 2nd degree relatives), and
- Rendering laboratory is a qualified provider of service per the Health Plan policy.
- Tiered Testing Strategy†,3
  - Tier 1
    - PMP22 deletion/duplication testing for CMT1A
    - GJB1 sequencing for CMTX1(except when there is known male to male transmission)
  - Tier 2
    - If negative for Tier 1 mutations, Tier 2 may be tested
    - MPZ sequencing for CMT1B
    - PMP22full sequencing for point mutations for CMT1E
  - Tier 3
    - If negative for Tier 1 and Tier 2 mutations, Tier 3 may be tested
- \textit{LITAF} sequencing for CMT1C
- \textit{EGR2} sequencing for CMT1D
- \textit{NEFL} sequencing for CMT1F and CMT2E

\textbf{CMT2 Testing}\footnote{†}

\textit{Rationale:} The proportion of CMT2 phenotypes, which is characterized by axonal (non-demyelinating) peripheral neuropathy, is 10-15\% of all CMT cases.\footnote{1} There are at least sixteen genes identified with CMT2 phenotypes; however 20\% of mutations have been attributed to the \textit{MFN2} gene. The gene-specific prevalence of other CMT2-associated mutations is unknown.\footnote{1}

- Genetic Counseling:
  - Pre and post-test counseling by a medical geneticist, genetic counselor, or other specialist as deemed by Health Plan policy, AND
- Previous Genetic Testing:
  - No previous genetic sequencing for mutation(s)/genes requested, and
  - No known familial mutation for CMT, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Clinical diagnosis or suspected diagnosis of CMT2, and
  - Sural nerve biopsy indicates that diagnosis is CMT of non-demyelinating type, or
  - Mild CMT symptoms, and
    - Normal NCV studies, or
    - EMG testing indicates axonal neuropathy, or
    - Greatly reduced compound motor action potentials, OR
  - Predisposition Testing or Carrier Screening:
    - Clinical diagnoses of CMT2 in two generations (1	extsuperscript{st} or 2	extsuperscript{nd} degree relative), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.
- Tiered testing strategy\footnote{1,3}
  - Tier 1
    - \textit{MFN2} sequencing for CMT2A2 autosomal dominant axonal neuropathy
    - \textit{GJB1} sequencing for autosomal dominant axonal neuropathy (except when there is known male to male transmission)
  - Tier 2
    - If Tier 1 is negative, Tier 2 may be tested
    - \textit{MPZ} sequencing
  - Tier 3
    - If Tier 2 is negative, Tier 3 may be tested
      - \textit{GDAP1}
      - \textit{GARS}
      - \textit{NEFL}
      - \textit{RAB7}
      - \textit{HSPB1}
CMT4 Testing†

_Rationale:_ CMT4 phenotypes are rare, but early age of onset may be characteristic of an autosomal recessive inheritance pattern most commonly associated with mutations of the _GDAP1_, _EGR2_, or _PRX_ genes.¹

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist, genetic counselor, or other specialist as determined by Health Plan policy, AND
- Previous Genetic Testing:
  - No previous genetic testing for the mutation(s) requested, and
  - No known familial mutation for CMT, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Early-onset of CMT symptoms (infancy – adolescence), and
  - Clinical diagnosis or suspected diagnosis of CMT4, OR
- Carrier Screening:
  - Partner of the individual is a known carrier of an autosomal recessive form of CMT, or
  - Evidence of possible autosomal recessive inheritance (i.e. only 1st degree siblings affected), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.
- Tiered testing strategy¹,³
  - Tier 1
    - _GDAP1_ for autosomal recessive CMT4A
  - Tier 2
    - If negative for _GDAP1_, then Tier 2 may be tested
    - _PRX_ for autosomal recessive demyelinating CMT4F
    - _EGR2_ Complete CMT Evaluation (Athena Diagnostics)

_Rationale:_ American Academy of Neurology guidelines recommend genetic testing that is “guided by the clinical phenotype, inheritance pattern (if available), and electrodiagnostic features (demyelinating and axonal).”³ The AAN recommends that genetic testing is focused on the most common abnormalities, including _PMP22_, _GJB1_, and _MPZ_, which account for 90% of CMT mutations. The AAN does not support complete panels of all known CMT genes, but rather recommends a stepwise evaluation method to improve genetic screening efficiency.³ Therefore, small panels of testing based on inheritance pattern or electrodiagnostic features may be appropriate, but _complete panels of all known CMT genes are not covered_.

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<table>
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<tr>
<th>NCD/LCD Jurisdiction and CPT Codes</th>
<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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References

Chromosome Abnormality, Fetal (Non-Invasive Prenatal Testing)

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<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Procedure Code(s)</th>
<th>Requires:</th>
<th>Lab Procedure Restrictions†</th>
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<tr>
<td>Fetal chromosomal aneuploidy (eg, trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21</td>
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</table>

* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

What Is a Chromosome Abnormality?

- Humans usually have 23 pairs of chromosomes. Each chromosome has a characteristic appearance that should be the same in each person.
- A chromosome abnormality is any difference in the structure, arrangement, or amount of genetic material packaged into the chromosomes. ¹
- Chromosome abnormalities can lead to a variety of developmental and reproductive disorders. Common chromosome abnormalities that affect development include Down syndrome (trisomy 21), trisomy 18, trisomy 13, Turner syndrome, and Klinefelter syndrome.
- About 1 in 200 newborns has some type of chromosome abnormality² and a higher percentage of pregnancies are affected but lost during pregnancy. About 6%-11% of stillbirths or neonatal deaths are associated with a chromosome abnormality.³
- The risk of having a child with an extra chromosome, notably Down syndrome, increases as a woman gets older.³ Historically, invasive prenatal diagnosis was only offered to women over the age of 35. However, many babies with Down syndrome are born to women under 35. Prenatal screening for Down syndrome and certain other chromosome abnormalities is now routinely...
offered to all pregnant women. As a result, prenatal diagnosis is now an option for most pregnant women.

Test Information

- Non-invasive prenatal testing (NIPT) is performed on a maternal plasma sample collected after approximately 9-10 weeks’ gestation.\(^4\)
- Testing methodology relies on the presence of cell-free fetal DNA in maternal circulation.\(^4\)
  Approximately 10% of DNA in maternal circulation is of fetal origin.\(^5\)
- Next-generation sequencing analysis is performed on this DNA to identify pregnancies at high risk for chromosomal aneuploidy. Detection rates for trisomies 21, 18, and 13 are greater than 98%, with false positive rates of less than 0.5%.\(^4\)
- Some laboratories also test for sex chromosome aneuploidies (such as Turner syndrome or Klinefelter syndrome) as well as rare chromosome microdeletion syndromes, with variable performance.
- Each commercial laboratory offering NIPT has a proprietary platform and bioinformatics pipeline:
  - The MaterniT21™ PLUS test developed by Sequenom Laboratories
  - The Harmony™ test developed by Ariosa Diagnostics
  - The verifi® test developed by Verinata Health
  - The Panorama™ test developed by Natera
- Chromosome analysis on invasive diagnostic testing (CVS and amniocentesis) is also routinely available for assessment of fetal chromosome abnormalities in pregnancy.

Guidelines and Evidence

- In 2012, The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM) jointly recommended cell free fetal DNA as one option that can be used as a primary screening test in women at increased risk of aneuploidy.\(^4\)
  - Indications for considering the use of cell free fetal DNA include (directly quoted):
    - Maternal age 35 years or older at delivery
    - Fetal ultrasonographic findings indicating an increased risk of aneuploidy
    - History of a prior pregnancy with a trisomy
    - Positive test result for aneuploidy, including first trimester, sequential, or integrated screen, or a quadruple screen
    - Parental balanced Robertsonian translocation with increased risk of fetal trisomy 13 or 21
  - “Cell free fetal DNA testing should not be offered to low-risk women or women with multiple gestations because it has not been sufficiently evaluated in these groups.”
  - “Cell free fetal DNA does not replace the accuracy and diagnostic precision of prenatal diagnosis with CVS or amniocentesis, which remain an option for women.”
- The International Society for Prenatal Diagnosis (ISPD) first issued a position statement on NIPT in January 2011 and then updated its recommendations in April 2013. ISPD summarizes that:\(^6\)
  - NIPT for aneuploidy screening can be helpful for women determined to be high-risk by other screening methods, maternal age, or family history.
"Analytic validity trials have been mostly focused on patients who are at high risk on the basis of maternal age or other screening tests. Efficacy in low risk populations has not yet been fully demonstrated."

"The tests should not be considered to be fully diagnostic and therefore are not a replacement for amniocentesis and CVS. Some affected pregnancies may not be detected and there may be false-positive results."

"There is insufficient information to know how well the test will perform in multiple gestation pregnancies that are discordant for trisomy but, theoretically, the detection of affected pregnancies could be lower than in singletons."

- The National Society of Genetic Counselors’ (NSGC, 2013) practice guideline includes NIPT as an option for patients at increased risk for chromosome aneuploidy:7
  - "Patients who desire screening information may be offered NIPT due to the high detection rates and low false positive rates. NIPT should only be offered in the context of informed consent, education, and counseling by a qualified provider, such as a genetic counselor. Standard confirmatory diagnostic testing should be offered as follow-up to positive NIPT results. High risk patients who decline NIPT but remain interested in screening should be made aware of alternate screening options as appropriate based on gestational age and screening availability."

- The American College of Medical Genetics and Genomics (ACMG, 2013) published a policy statement regarding Non Invasive Prenatal Screening (NIPS), stating “although studies are promising and demonstrate high sensitivity and specificity with low false positive rates, there are limitations to NIPS.” Due to the limitations outlined in the policy statement, ACMG states that “invasive testing is recommended for confirmation of a positive screening test and should remain an option for patients seeking a definitive diagnosis. In addition to limitations of NIPS, the policy provides clear recommendations for the components of pre- and post-test genetic counseling. The policy statement does not, however, provide guidance regarding to whom NIPS should be offered. 5

- Early evidence for the performance of NIPT in the low-risk population was published by Bianchi and colleagues in the New England Journal of Medicine in February 2014.8 Following this publication, The Society for Maternal Fetal Medicine (SMFM, 2014) reiterated its position that NIPT should be limited to high-risk pregnancies, stating: “SMFM has reviewed the evidence, including this recent paper, and feels that while NIPT is a promising new technology, and this new report is important and excellent news, it is not enough to change current ACOG and SMFM recommendations. Given that just eight aneuploidies were present in the entire cohort of patients, the true test performance is difficult to determine.”9

Criteria

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND.

- Previous Genetic Testing:
  - No previous cell free fetal DNA testing already performed during this pregnancy, and
  - No previous karyotyping, aneuploidy FISH, and/or array CGH already performed during this pregnancy, AND

- Diagnostic or Predisposition Testing:
Cell-free fetal DNA-based prenatal screening for fetal aneuploidy (trisomy 13, 18, and 21) is considered medically necessary when all of the following criteria are met:

- Singleton pregnancy, and
- Gestational age within the window validated by the selected testing laboratory, and
- At least one of the following increased risk indications:
  - Advanced maternal age defined as 35 years or older at delivery*, or
  - Abnormal first or second trimester screening result (nuchal translucency or maternal serum) associated with an increased risk for a chromosome abnormality detectable by NIPT, or
  - Fetal ultrasound findings that suggest an increased risk for a chromosome abnormality that is detectable by NIPT**, or
  - Previous pregnancy with a chromosome abnormality detectable by NIPT*, or
  - Parental chromosome abnormality associated with an increased risk for a chromosome abnormality detectable by NIPT* (e.g., balanced Robertsonian translocation of chromosome 13 or 21), AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

- Additional testing:
  - Cell-free fetal DNA-based prenatal screening for aneuploidy of the X and Y chromosomes, detection of microdeletion syndromes, detection of Trisomy 16 or 18, or any additional testing beyond screening for aneuploidy of chromosomes 13, 18, and 21 is not considered medically necessary.
  - Additional CPT codes or additional units billed for such test enhancements will not be reimbursed.

- Additional prenatal diagnostic testing:
  - Prenatal diagnosis by amniocentesis or CVS following NIPT is generally only indicated when NIPT results are abnormal or additional information becomes available throughout the pregnancy that suggests additional risk factors. Amniocentesis and/or CVS billed after NIPT are subject to medical necessity review.

*If conceived by egg and/or sperm donor, these indications must apply to the biological relationship

**Prenatal diagnosis by amniocentesis or CVS is recommended when the fetus has a structural birth defect

References

Chromosomal Microarray (CMA): Developmental Abnormalities

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<th>Procedure(s) covered by this policy:</th>
<th>Procedure Code(s)</th>
<th>Requires:</th>
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Click here for applicable Medicare NCD/LCD information

Description

- Developmental disorders, such as intellectual disability (ID) and congenital birth defects are common, affecting approximately 3-4% of the general population. Autism spectrum disorders (ASD), including pervasive developmental delay (PDD), are of increasing concern, with recent CDC incidence figures estimating 1 in 155 affected children.
- Etiology of developmental disorders is complex. While some may be caused by environmental factors, such as injury and infection, genetic causes play a significant role and must be evaluated.
- Major structural birth defects can often be identified prenatally by ultrasound evaluation, while some minor anomalies and ID cannot.
- Chromosome analysis (karyotyping) has historically been a first line test in the evaluation of most intellectual and physical developmental disorders in which a clear etiology could not be established on the basis of clinical findings, either during pregnancy or after birth. However, small deletions and duplications of genetic material that cannot be detected through karyotyping account for a significant proportion of these developmental disorders. These changes are called "copy number variants" (CNVs). CNVs are detected using chromosome microarray (CMA) testing. CMA is known by several names including array-comparative genomic hybridization (aCGH) and single-nucleotide polymorphism arrays (SNP-array).
- While there are significant advantages of CMA over conventional karyotyping with regard to diagnostic yield, there are disadvantages as well. Limitations of CMA include the inability to detect 1) balanced translocations or inversions, 2) certain forms of polyploidy, 3) low level mosaicism, and 4) some marker chromosomes. Additional disadvantages of CMA include the detection of CNVs of uncertain clinical significance, the inability to differentiate free trisomies from unbalanced Robertsonian translocations, and the high cost of testing as compared to traditional karyotyping.
- There is a paucity of US data related to cost effectiveness of CMA vs. conventional karyotyping. A 2007 analysis on the cost effectiveness of microarray technology in the National Health Service of the United Kingdom concluded that in the context of idiopathic learning disability (ILD), it may be...
appropriate to utilize CMA as the first tier diagnostic. The authors concluded that “testing for genomic imbalances in ILD using microarray technology is likely to be cost-effective because long-term savings can be made regardless of a positive (diagnosis) or negative result. Earlier diagnoses save costs of additional diagnostic tests. Negative results are cost effective in minimizing follow up test choice.”

Pediatric/adult CMA testing
- Identifying an underlying genetic cause in individuals with ID/developmental delay (DD) or ASD may:
  - Provide diagnostic and prognostic information
  - Improve health screening and prevention, for some conditions
  - Allow for targeted testing of family members and accurate recurrence risk counseling
  - Empower the patient and family to acquire needed services and support
  - Limit additional diagnostic testing
  - Anticipate and manage associated medical co-morbidities
- Diagnostic yield for CMA differs based on clinical presentation. In general, CMA will detect significant abnormalities in 15-20% of individuals with DD/ID, as opposed to conventional karyotype (~3%).
  - Approximately 10-19% of people with unexplained ID or (DD) and/or MCA will have CNVs.
  - A diagnostic yield for ASD is estimated at 7-10%.
- CMA should not be used in cases of family history of chromosome rearrangement in phenotypically normal individuals or in individuals experiencing multiple miscarriages.

Prenatal CMA testing
- Chromosomal microarray on chorionic villi or amniocytes is indicated in a pregnancy identified with one or more major structural abnormalities. Identifying an underlying genetic cause in these pregnancies may:
  - Provide diagnostic and prognostic information
  - Guide prenatal management and decision-making
  - Allow for targeted testing of family members and accurate recurrence risk counseling
- Diagnostic yield of CMA testing differs based on clinical presentation. The results of one recent multicenter trial of CMA in the prenatal setting were published in 2012. This study reported that CMA identified a clinically relevant deletion or duplication in 6% of prenatal cases with a structural anomaly and normal karyotype. In addition, 1.7% of prenatal cases with an indication of advanced maternal age or positive screening results and normal karyotype had a clinically relevant deletion or duplication identified by CMA.
- In a large series of fetuses with ultrasound anomalies and normal conventional karyotype, CMA detected chromosome abnormalities in 5% of fetuses and up to 10% in those with 3 or more anatomic abnormalities.

Test Information
- Chromosome microarray (CMA) testing generally works by fluorescently tagging DNA from a patient test sample with one color and combining it with a control sample tagged with a different color. The two samples are mixed and then added to the array chip, where they compete to hybridize with the DNA fragments on the chip. By comparing the patient test sample versus the
control, computer analysis can determine where genetic material has been deleted or duplicated in the patient.

- There are a growing number of CMA testing platforms, including non-chip based applications, which differ in approach and resolution. Testing guidelines do not endorse one CMA over another.7,8,4 However, international consensus guidelines do suggest that CMAs should have coverage better than that offered by a standard karyotype (~5 Mb), and resolution of ≥400 kb throughout the genome.7

- CMAs typically include the subtelomeric regions and all known chromosome microdeletion syndrome regions, such as those for 22q11.2 (DiGeorge) syndrome, Williams syndrome (7p11.2), and Smith-Magenis syndrome (17p11.2). Therefore, subtelomeric and disease-specific FISH tests are not needed in parallel with CMA, or as follow-up to normal CMA results.

- If a unique CNV is detected in a fetus, it is usually necessary to test both parents to determine whether the CNV is inherited or a new (de novo) genetic change. This information along with parental findings can be used to weigh the possibilities of a benign vs. pathogenic variant. However, even with parental studies, the clinical outcome may remain unclear.13 A de novo variant is more likely to represent a pathologic abnormality.3,13

- In contrast to typical chromosome analysis, CMA testing does not require dividing cells in culture. This makes testing possible in samples from perinatal losses, which are often difficult tissues to culture.3,13

Among stillborn infants, microarray analysis has a higher likelihood of obtaining a result and identifying underlying genomic abnormalities as compared to karyotyping.14

Guidelines and Evidence

- The American College of Obstetricians and Gynecologists Committee on Genetics and the Society for Maternal-Fetal Medicine (2013) published a committee opinion regarding the application of chromosomal microarray in the prenatal setting. This opinion recommended that CMA replaces fetal karyotyping for “patients with a fetus with one or more major structural anomalies identified on ultrasonographic examination and who are undergoing invasive prenatal diagnosis”.13

- American Academy of Neurology and the Practice Committee of the Child Neurology Society (2011) published a practice parameter for the evaluation of global developmental delay. The authors state that “Microarray is the genetic test with the highest diagnostic yield in children with unexplained GDD/ID.”6

- The American College of Medical Genetics (2010) Professional Practice and Guidelines Committee recommends CMA as a first-tier test for the evaluation of “multiple anomalies not specific to a well-defined genetic syndrome, apparently non-syndromic developmental delay/intellectual disability, and autism spectrum disorders.”6

- The International Standard Cytogenomic Array Consortium (2010) recommends offering CMA as a first-tier genetic test, in place of karyotype, for patients with unexplaned developmental delay/intellectual disability, autism spectrum disorders, or birth defects.7
Criteria

Note: The following criteria do not address microarray testing for tumor samples or other hematology oncology indications.

Pediatric/Adult Chromosomal Microarray

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous CMA testing, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Diagnosis cannot be made on clinical evaluation alone, and
  - Common aneuploidy (Trisomy 13, 18, 21, or sex chromosome) is not a suspected diagnosis, and
  - One of the following presentations:
    - Apparently nonsyndromic DD/ID, or
    - Autism Spectrum Disorder, or
    - Multiple congenital anomalies not specific to a well-delineated genetic syndrome

†Multiple congenital anomalies defined as 1) two or more major anomalies affecting different organ systems or 2) one major and two or more minor anomalies affecting different organ systems. [Major structural abnormalities are generally serious enough as to require medical treatment on their own (such as surgery) and are not minor developmental variations that may or may not suggest an underlying disorder.]

* NOTE: Microarray is considered a first tier test in the evaluation of postnatal developmental disorders. Therefore, it often is not necessary to do chromosome analysis or FISH in conjunction with microarray. Microarray requests following such testing will require review.

Prenatal Chromosomal Microarray

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous CMA testing in the same pregnancy, AND
- Diagnostic Prenatal Testing:
  - One or more major structural abnormality identified on ultrasound
  - Structurally normal fetus from a high risk pregnancy. Indications for high risk include:
    - Advancing maternal age
    - Abnormal first or second trimester nuchal translucency or maternal serum screening result
    - Previous pregnancy with a chromosome abnormality
    - Parental chromosome abnormality
    - Family history of known or suspected chromosome problem
Pregnancy was conceived after preimplantation genetic diagnosis (PGD) and intracytoplasmic sperm injection (ICSI) due to male-factor infertility.

Major structural abnormalities are generally serious enough as to require medical treatment on their own (such as surgery) and are not minor developmental variations that may or may not suggest an underlying disorder, which include but are not limited to “soft markers” on ultrasound such as echogenic intracardiac focus, choroid plexus cysts, and single umbilical artery.

Microarray may also be used in association with in utero fetal demise, stillbirth, or neonatal death. If microarray will be performed on fetal tissue after delivery, reference the pediatric/adult policy. If microarray will be used on amniocentesis, CVS, or PUBS samples, reference the prenatal policy.

Exclusions and Other Considerations

- CMA should not be used in cases of family history of chromosome rearrangement in phenotypically normal individuals
- CMA should not be used in individuals experiencing multiple miscarriages.
- If routine karyotype and CMA are ordered simultaneously, only the most appropriate test based on clinical history will be considered for coverage.
- Full karyotype in addition to CMA is considered excessive in the prenatal diagnosis setting. However, a limited 5 cell analysis will be approved in addition to CMA if criteria for CMA are met. This approval will be subject to claims review to ensure that the appropriate number of units for a limited 5 cell analysis is billed.
- If CMA has been performed, the following tests are often excessive and are not considered medically necessary. Each test may require prior authorization or medical necessity review during the claims process.
  - Routine karyotype
  - FISH analysis
  - Telomere analysis
  - More than one type of microarray analysis (i.e. if 81228 performed, 81229 is not medically necessary)

### NCD/LCD Jurisdiction and CPT Codes

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400 Buckwalter Place Boulevard, Bluffton, SC 29910 • (800) 918-8924 www.carecorenational.com
References


Cowden Syndrome

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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Click here for applicable Medicare NCD/LCD information

Description

- Cowden syndrome (CS) is a rare hereditary cancer syndrome usually caused by a mutation in the PTEN gene.
- Cowden syndrome is characterized by an increased risk for benign and malignant tumors of the breast, endometrium, and thyroid (non-medullary). Other common features include macrocephaly and growths on the skin or mucous membranes (mucocutaneous lesions). The International Cowden Consortium clinical diagnostic criteria are fulfilled when any one of the following is met:
  - A combination of characteristic mucocutaneous lesions:
    - Six or more facial papules of which three or more must be trichilemmomas (skin tags)
    - Facial papules and oral mucosal papillomatosis
    - Oral mucosal papillomatosis and acral keratoses
    - 6 or more palmo-plantar keratoses
  - Two or more major* criteria
  - One major* and three or more minor** criteria
  - Four or more minor** criteria.
- An online tool calculates the likelihood of identifying a PTEN mutation based on clinical findings: http://www.lerner.ccf.org/gmi/ccscore/
- People with Cowden syndrome need heightened cancer surveillance starting at age 18.2
  - The lifetime risk for breast cancer is 25-50% with an average age at diagnosis of 38-46 years.1
  - The lifetime risk for thyroid cancer is about 10%. Benign thyroid growths are also found in up to 75% of people with Cowden syndrome.1
  - Endometrial cancer has an estimated 5-10% lifetime risk, although this is not well-defined.1
  - The gastrointestinal polyp risk (often colonic) in patients with Cowden syndrome may be 80% or higher. Early onset colorectal cancer has been reported in 13% of patients with PTEN associated Cowden syndrome suggesting routine colonoscopy may be warranted in this population.2,4,5
- Lhermitte-Duclos disease (LDD) is a rare, benign tumor of the cerebellum called dysplastic gangliocytoma that may present in childhood or adulthood. Most adult-onset LDD is caused by a PTEN mutation even when no other signs of Cowden syndrome are present.1
• Prevalence is estimated to be 1 in 200,000 individuals although Cowden syndrome is believed to be underdiagnosed. Nearly all people with a Cowden syndrome mutation will develop symptoms (complete penetrance).

• Cowden syndrome is inherited in an autosomal dominant manner, meaning that a person only needs a mutation in one copy of the gene to be affected. A child of an affected person has a 50% chance to inherit the mutation.

• PTEN hamartoma syndrome (PHTS) is sometimes used to describe the group of conditions caused by PTEN mutations that include hamartomatous growths: Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, and Proteus-like syndrome.

• Up to three methodologies may be used to identify a disease-causing mutation for the first person with Cowden syndrome to be tested in the family.
  o **Complete gene sequencing** is required because mutations occur throughout the gene. Such testing will detect a mutation in about 80% of people with a clinical diagnosis of Cowden syndrome.
  o **Deletion/duplication analysis** can be used in cases where a mutation is not found by sequencing. The likelihood of identifying a deletion or duplication in people with clinically diagnosed Cowden syndrome is unknown, but expected to be relatively low.
  o Additionally, **sequencing of the promoter region** may be available as a separate test or as part of complete gene sequencing. Sequencing the promoter region will detect an additional 10% of PTEN mutations that cause Cowden syndrome. Once the familial mutation is identified, testing for that one mutation (often called single site analysis) can be offered to at-risk relatives. Such testing is much less expensive than complete gene testing and the results are highly reliable.

• Evidence-based guidelines (Category 2A) from the *National Comprehensive Cancer Network (NCCN, 2011)* support the use of PTEN genetic testing in those clinically diagnosed with Cowden syndrome. They recommend PTEN genetic testing in any of the following situations:
  o Family history of a known PTEN mutation (single site PTEN testing is appropriate)
  o A personal history of any of the following:
    - Bannayan-Riley-Ruvalcaba syndrome (BRRS)
    - Adult-onset Lhermitte Duclos disease (cerebellar dysplastic gangliocytoma)
    - Autism spectrum disorder and macrocephaly (≥97th percentile)
    - Two or more biopsy proven trichilemmomas
    - Macrocephaly and at least one other major* criteria
    - Three major* criteria without macrocephaly
    - One major* and three or more minor** criteria
    - Four or more minor** criteria
  o At-risk relative of someone clinically diagnosed with Cowden syndrome or BRRS (who has not had genetic testing), when the at-risk relative has at least one major* or two minor** criteria. Ideally, the at-risk person is a first-degree relative (parent, sibling, child) of someone clinically diagnosed, but testing more distant relatives is acceptable if closer relatives are not available or willing to have testing.
Criteria

PTEN gene testing may be considered in individuals with a suspected or known clinical diagnosis of Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome (BRR), or a known family history of a PTEN mutation.

Testing may be considered for individuals whose medical and/or family history is consistent with ANY of these:

- A relative with a known deleterious PTEN gene mutation; OR
- Personal history of ANY of the following:
  - Bannayan Riley-Ruvalcaba syndrome; OR
  - Adult Lhermitte-Duclos disease (LDD); OR
  - Autism spectrum disorder and macrocephaly; OR
  - At least two biopsy-proven trichilemmomas; OR
  - At least two major criteria* (one must be macrocephaly); OR
  - Three major criteria* without macrocephaly; OR
  - One major and at least three minor criteria*; OR
  - Four or more minor criteria*
- At-risk person with a family history of:
  - A relative (includes first-degree relative or more distant relatives if the first-degree relative is unavailable or unwilling to be tested) with a clinical diagnosis of Cowden syndrome or BRR (no previous genetic testing); AND
  - One major OR two minor criteria* in the at-risk person

*Criteria for testing purposes are:

Major:

- Breast cancer
- Mucocutaneous lesions
  - One biopsy-proven trichilemmoma
  - Multiple palmoplantar keratoses
  - Multifocal or extensive oral mucosal papillomatosis
  - Multiple cutaneous facial papules (often verrucous)
  - Macular pigmentation of glans penis
- Macrocephaly (97th percentile or greater; 58 cm in adult women, 60 cm in adult men)
- Endometrial cancer
- Non-medullary thyroid cancer
- Multiple GI hamartomas or ganglioneuromas

Minor:

- Other thyroid lesions (e.g., adenoma, nodule(s), goiter)
- Mental retardation (IQ<75)
- Autism spectrum disorder
- Single GI hamartoma or ganglioneuroma
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- Renal cell carcinoma
- Uterine fibroids
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**References**

Cutaneous Malignant Melanoma

### Description

Melanoma is a malignancy of melanocytes that occurs in the skin, eyes, ears, gastrointestinal tract, leptomeninges, and oral and genital mucous membranes. It is the most aggressive form of skin cancer and has the ability to metastasize to any organ, including the brain and heart. In the U.S., cutaneous malignant melanoma (CMM) is the fifth most common cancer in men and the sixth most common cancer in women. The incidence of malignant melanoma is increasing worldwide. In 2009, the lifetime risk of developing melanoma was 1 in 55 in the U.S. This represents a 10-fold increase in the last 50 years. The median age at diagnosis is 57 years, and the median age at death is 67 years. Males are approximately 1.5 times more likely to develop melanoma than females. The most common areas to be affected are the back for men and the arms and legs for women.

The etiology of CMM is complex. Over the past two decades, epidemiologic studies of melanoma have identified major environmental, phenotypic, and genetic risk factors. These factors, individually and in combination, determine the risk for melanoma. The major environmental risk factor for melanoma is exposure to ultraviolet radiation. Epidemiologic data suggest that the risk for CMM is due in part to a complex relationship between sun exposure and a person's response to sun exposure. People who suntan poorly, sunburn easily, or who have had multiple or severe sunburns have a 2- to 3-fold increased risk for developing CMM. Intense intermittent sun exposure at any age appears to confer a greater risk for CMM (OR = 1.6 to 1.7), than chronic, or constant occupational sun exposure (OR = 0.7). The high doses of UVA received in tanning beds and with exposure to psoralen and UVA therapy for psoriasis and other skin conditions also increases the risk for melanoma.

There is an inverse correlation between the risk for melanoma and skin color. Caucasian individuals are 10-times more likely to develop CMM than darker-skinned individuals (i.e. African Americans, darker Hispanics, and Asians). Other characteristics that increase the risk for melanoma include red or blonde hair, light eye color, freckles, an inability to tan and multiple nevi. Individuals with multiple atypical nevi, regardless of their personal and/or family history of melanoma are significantly more likely to develop melanoma when compared to patients without atypical nevi. People affected by certain genetic conditions also have an increased risk for melanoma; these conditions include xeroderma pigmentosa, retinoblastoma, Li-Fraumeni syndrome, hereditary breast and ovarian cancer syndrome due to BRCA2 mutations, and Werner syndrome. Age is an additional risk factor for CMM. Having a personal history of basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) increases the risk for melanoma, although the actual risk is not clear.

If a person has a history of sporadic melanoma, the risk for a second primary melanoma is approximately 5%. However, the risk increases for people with additional risk factors, such as intensive sun exposure...
early in life, the presence of multiple atypical nevi, fair skin, a family history and gene mutations which result in a predisposition to melanoma.\textsuperscript{24} If there is a family history of melanoma, the risk of a second primary tumor is approximately 30\%.\textsuperscript{25-28}

About 5\% to 12\% of CMMs develop in individuals with at least one affected first-degree relative, suggesting that family history of CMM is a major risk factor.\textsuperscript{29} Familial melanoma likely occurs by chance as well as by shared genetic and non-genetic factors, such as hair color, type of nevi, mutations in melanoma susceptibility genes, and exposure to the sun. In familial melanoma, when compared to non-familial melanoma, the age at diagnosis is typically earlier, lesions are generally thinner, and there is a higher frequency of multiple primary melanomas. However, the lesions are histologically similar and the clinical course is not significantly different.\textsuperscript{29} Over the years several terms have been used to describe familial CMM including: B-K mole syndrome, familial atypical multiple mole melanoma syndrome (FAMMM), hereditary dysplastic nevus syndrome, and classic atypical-mole syndrome.\textsuperscript{18} Specific features have consistently been reported in hereditary CMM families. These features include multiple primary melanomas in a single individual, early age of onset of initial cutaneous melanoma, vertical transmission, and in some families, increased rates of pancreatic cancer.\textsuperscript{18,30}

By studying families with several affected family members, germline mutations in cyclin-dependent kinase inhibitor 2A (\textit{CDKN2A}) (OMIM*600160) and cyclin-dependent kinase 4 (\textit{CDK4}) (OMIM*123829) have been identified, which appear to confer an increased susceptibility to CMM.\textsuperscript{31-33} Currently, \textit{CDKN2A} and \textit{CDK4} are the only high-risk melanoma susceptibility genes that have been discovered. Both genes exhibit autosomal dominant inheritance patterns. Given that \textit{CDKN2A} and \textit{CDK4} mutations are present in only a subset of familial melanoma kindreds, it is likely that other high-risk melanoma susceptibility genes exist. Previous family studies using linkage analysis identified regions on chromosome 1p22 and 1p36, suggesting the possibility of additional melanoma susceptibility genes in these locations.\textsuperscript{34,35} There also appears to be additional susceptibility loci in the 9p21 region.\textsuperscript{36} However, no other high-risk melanoma susceptibility genes have yet been found.

\textit{CDKN2A} is found to be mutated in approximately 35\% to 40\% of people with familial melanoma.\textsuperscript{37,38} Mutations reported in the \textit{CDKN2A} gene include nonsense and missense mutations, small deletions and insertions.\textsuperscript{39,40} Large deletions of one or more exons of the \textit{CDKN2A} gene have been reported in association with familial melanoma, however they are rare.\textsuperscript{41} Only a small number of mutations have been reported in the \textit{CDK4} gene and all of the mutations reported to date have been found in exon 2.\textsuperscript{40}

As the number of melanoma cases in a family increases, the frequency of mutations also increases. The frequency of detectable mutations is less than 5\% for families from North America, Europe, and Australia with only 2 affected members. Individuals from North America, Europe, and Australia with 3 or more affected family members have a 20\% to 40\% chance of having a detectable \textit{CDKN2A} gene mutation, and it increases to greater than 50\% for families with more than 6 affected members.\textsuperscript{17,29} \textit{CDK4} mutations have only been found in 6 melanoma families worldwide and account for less than 3\% of all cases of melanoma.\textsuperscript{42,43}

In a 2009 study of a total of 204 Italian melanoma families researchers found that 33\% (68/204) of the families overall, and 25\% (36/145) of those with just two affected members, carried mutations in \textit{CDKN2A}.\textsuperscript{44} In families with 3 cases of melanoma the mutation frequency was 46\% (19/41), and in the families with more than 4 affected family members it reached 72\% (n=13).\textsuperscript{45} The frequency of mutations also increased significantly with the number of patients with multiple primary melanomas (MPM) in the
family and reached 100% in families with two or more MPM, confirming that the number of cases with MPM increases the likelihood of detecting a germline \textit{CDKN2A} mutation in a family.\textsuperscript{38,44,46,47} Mutation testing revealed that none of the families carried mutations in \textit{CDK4}.\textsuperscript{44}

Estimates of \textit{CDKN2A} mutation penetrance have varied greatly (28-91%) depending on the study design as well as ethnic background, regional UV intensity, and coinheritance of variants in \textit{MC1R}, a low penetrance susceptibility gene.\textsuperscript{25,48} The International Melanoma Genetics Consortium performed the largest family-based evaluation of penetrance in \textit{CDKN2A} mutations carriers.\textsuperscript{48} They analyzed 80 families with documented \textit{CDKN2A} mutations and multiple family members with CMM from Europe, Australia, and the United States. Overall, \textit{CDKN2A} mutation penetrance was estimated to be 30% (95% CI = 0.12 to 0.62) by age 50 years and 67% (95% CI = 0.31 to 0.96) by age 80 years. However, penetrance was significantly modified by geographic location. By age 80 years, penetrance reached 58% in Europe, 76% in the United States, and 91% in Australia.\textsuperscript{48} The risk appears to vary between countries and families, and it is not yet clear whether this variation results from the type of mutation, coinheritance with other genetic variations, environmental exposures, or other as yet identified genetic variables.

The mean age at diagnosis of melanoma in individuals who carry a \textit{CDKN2A} mutation worldwide is in the 30s and 40s, whereas the mean age at diagnosis in high-risk families without a \textit{CDKN2A} mutation is in the 40s and 50s.\textsuperscript{30} In the U.S., the mean age at diagnosis of melanoma in known \textit{CDKN2A} mutation carriers is 35 years (range 14-68 years) compared to a median age of 57 years in the general population.\textsuperscript{2,48}

A correlation has been established between the presence of mutations and pancreatic cancer risk in some families.\textsuperscript{29,30,38,49,50} Within families that demonstrate a predisposition to pancreatic cancer, the relative risk for pancreatic cancer ranges from 9.4 (95% CI 2.7-33.4) to 47.8 (95% CI 28.4-74.7).\textsuperscript{30,49} In families who are positive for \textit{CDKN2A} mutations in the Netherlands, the risk of developing pancreatic cancer by age 80 years is 25%.\textsuperscript{30}

The alpha melanocyte-stimulating hormone receptor (\textit{MC1R}) gene is located on chromosome 8. It codes for the receptor through which signaling for melanin production occurs. Partial loss-of-function mutations are associated with red hair, fair skin, and poor tanning, and increased skin cancer risk independent of cutaneous pigmentation.\textsuperscript{51,52} It is the most common gene yet identified, which confers a weak susceptibility to melanoma even in patients without red hair. There are other possible low penetrance genes promoting susceptibility to melanoma which the Melanoma Genetics Consortium and others are exploring.

Several laboratories offer tests for identifying germline mutations in \textit{CDKN2A} and \textit{CDK4} (\url{www.genetests.org}). Genetic testing involves bi-directional sequencing of the three coding exons and the intron/exon boundaries including the g.-34T promoter mutation. Some laboratories use MLPA to look for large deletions and duplications of the \textit{CDKN2A} gene.\textsuperscript{53}

Expert opinion regarding testing for germline mutations of \textit{CDKN2A} in familial melanoma follows two divergent schools of thought. Arguments for genetic testing include the value of identifying a cause of disease for the individual tested, improved motivation for sun protection and skin surveillance, a lowered threshold for biopsying suspicious lesions, and early detection, which has the potential to save lives because of the exceptionally good outcome for thin melanomas and poor prognosis for advanced melanomas.\textsuperscript{17,24,54-56} The 5-year survival rate is 99% for localized melanoma, 5-year survival rates for regional and distant-stage disease are 65% and 15% respectively, and the reassurance of a negative test result in individuals in a family with a known mutation.\textsuperscript{57} However, a negative test result in a family that
does not have a known mutation is uninformative; the genetic cause of disease in these patients must still be identified.

Based on a review of the literature published between 1994 and 2007, members of the International Melanoma Genetics Consortium, a research consortium coordinated by the University of Leeds, concluded that “… individuals with three or more primary melanomas and/or families with at least one invasive melanoma and two or more other diagnosis of melanoma and/or pancreatic cancer in aggregate among first- or second-degree relatives on the same side of the family are appropriate candidates for a genetic evaluation”. The consensus is that individuals at high risk should be referred for genetic counseling and allowed to weigh the pros and cons of testing, and that they will benefit from tailored education and screening. Genetic testing for mutations associated with susceptibility to malignant melanoma is also appropriate for unaffected individuals who have a first-degree relative who has tested positive for a deleterious mutation. While there is limited data on the impact of \textit{CDKN2A} genetic testing, Aspinwall et al. found an increase in screening and precautionary behavior among both mutation-positive and mutation-negative patients. After receiving their test results, 55% patients reported adopting at least one screening behavior.

Arguments against genetic testing include the fact that individuals who test negative for a known \textit{CDKN2A} mutation remain at increased risk for melanoma; presumably because they could have inherited other less penetrant susceptibility genes and the fact that they share common environmental risk factors. Therefore the precautions in the preceding paragraph would apply regardless of mutation status. A second argument against testing in families with inherited \textit{CDKN2A} mutations is the rate of CMM in non-carriers has been reported to be as high as 9%. A third argument against genetic testing is that the identification of a \textit{CDKN2A} mutation does not affect the clinical management of the affected patient or their family members. These individuals still require close dermatologic follow-up, regardless of genetic testing result, and pancreatic cancer screening has unclear utility.

Currently, patients diagnosed with melanoma are treated similarly regardless of \textit{CDKN2A} mutation status. Individuals at high risk for melanoma should be educated about sun protection, avoidance of intense sun exposure, and other preventive measures, such as learning how to detect dysplastic nevi characteristics and the warning signs of melanoma. Management recommendations also include examination of the entire skin surface by a skilled healthcare provider every 6 months beginning at 10 years, or earlier, for suspicious nevi, until nevi are stable, and then annually thereafter. The American Academy of Dermatology and GenoMel also recommend that patients at risk for melanoma do skin self-examinations monthly. These two screening strategies are the major components of early detections programs in melanoma.

Given the present evidence and uncertain clinical utility, genetic testing for mutations associated with cutaneous malignant melanoma and predisposition testing for cutaneous malignant melanoma is not-covered and considered investigational. Referral for genetics consultation is recommended in individuals with three or more primary melanomas and/or families with at least one invasive melanoma and two or more other diagnosis of melanoma and/or pancreatic cancer in aggregate among first- or second-degree relatives on the same side of the family.

**Criteria**

Genetic testing is \textit{not} approved for malignant melanoma because it is considered experimental, investigational or is unproven.
### Cutaneous Malignant Melanoma

**NCD/LCD Jurisdiction and CPT Codes**

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**See LCD jurisdictions that refer to MolDX.**

LCD: MolDX

[http://www.palmettobga.com/palmetto/MolDX/nsfDocsCat/MolDx%20Website-MolDx-Browse%20By%20Topic-General~9BMLRK6738?open&navmenu=Browse^By^Topic][[1]]

**81404 MOPATH PROCEDURE LEVEL 5**

#### References


CYP2C19 for Clopidogrel Response

**Procedure covered by this policy:**

<table>
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<tr>
<th>Procedure</th>
<th>Procedure Code(s)</th>
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</thead>
<tbody>
<tr>
<td>Targeted Mutation Analysis of CYP2C19 Mutations</td>
<td>81225</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specific sequence to be followed or additional information is required and must be supplied by the lab performing procedure(s) for full claim payment.

Description

The CYP2C19 metabolic pathway metabolizes the platelet aggregation inhibitor clopidogrel (Plavix®) and is also responsible for metabolizing some antidepressants, barbiturates, proton pump inhibitors, antimalarial and antitumor drugs. The primary indication for use of clopidogrel is to decrease the risk of cardiovascular events in individuals with acute coronary syndrome (ACS) or atrial fibrillation, especially in patients with a history of percutaneous coronary intervention.\(^1\)\(^-\)\(^3\) Approximately 1.4 million patients are hospitalized every year presenting with primary or secondary ACS, for which clopidogrel is the most commonly prescribed therapy (along with aspirin) and is effective at preventing the clotting of platelets, reoccurrence of myocardial infarction (MI) or stroke in most individuals.\(^4\) However, negative cardiovascular events, such as MI and stroke do occur in patients on clopidogrel and current research suggests that this is due to a genetic trait that causes some individuals to ineffectively metabolize the drug into its active form. This genetic trait may leave these poor metabolizers (PMs) at an increased risk of cardiovascular event.

Current research is mixed about the clinical utility that a genetic test holds when determining an individual's CYP2C19 genotype, however in March 2010 the Food and Drug Administration (FDA) issued a box warning urging caution that PMs may not receive the full benefit of the drug and may still be at increased risk for MI, stroke, or cardiovascular death.\(^5\) The FDA advised that "healthcare professionals consider alternative dosing of Plavix for these patients, or consider using other antiplatelet medications,"\(^6\) and suggested genetic testing to determine the CYP2C19 genotype for the purpose of identifying those at risk for poor metabolism of the drug.\(^5\) The warning suggests that PMs may need alternative dosing or other medications; however, to date there are no guidelines or algorithm for treatment based on CYP2C19 genotype.

A large meta-analysis by Mega et al. (2010) found that the presence of one copy of a reduced-function allele (CYP2C19*2) was associated with significant increase in adverse cardiovascular events for patients using clopidogrel following PCI with stent thrombosis being the most common adverse event.\(^7\) However, Paré et al. (2010) genotyped individuals involved in clinical trials investigating the efficacy of clopidogrel in comparison to placebo and found that the effect of clopidogrel does not significantly differ between individuals with decreased-function alleles (CYP2C19*2 and CYP2C19*3) and those without alleles that decrease metabolism of the drug.\(^3\) Additionally, there are a number of alleles that have also been suggested to decrease the function of clopidogrel (e.g. *4, *5, etc.) and the CYP2C19*17 allele has been shown to increase metabolism of the drug, but none of these alleles are adequately studied with prospective clinical trials to determine if, in this case of pharmacogenetics, treatment can be catered to
genotype. Further complicating the implementation of the FDA guidelines is a lack of information surrounding treatment for individuals with only one decreased-function allele, or intermediate metabolizers²,³, and how to predict risk in the face of other factors that may impact platelet aggregation levels (ABCB1 and CYP3A4 genetic influence).

Thus, CYP2C19 genotyping is unable to sufficiently predict a level of risk for adverse cardiovascular event for an individual on clopidogrel therapy and the only method to determine if the drug is being adequately metabolized is – other than an actual adverse event – to measure platelet aggregation levels. Unfortunately the ability to do this at a screening or follow-up visit is limited as there are few products on the market for point-of-care platelet function assays.⁸

One cost-effectiveness study has calculated that the average annual savings that genetic testing for clopidogrel genotype provides was $120 per patient.⁴ This savings is, however, dependent upon the relationship between cost of genotyping and clopidogrel therapy. As the price of clopidogrel therapy goes down, the cost of genotyping must also decrease to maximize the cost-effectiveness of genetic testing. When generic forms of clopidogrel enter the market a considerable decrease in the cost for genetic testing is necessary to sustain this efficiency.

With the information provided, coverage for CYP2C19 genetic testing has been determined to be medically necessary for individuals for whom clopidogrel therapy has been recommended or those who are undergoing treatment with clopidogrel.

Criteria

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

- Previous Testing:
  - No previous genetic testing of CYP2C19, AND
- Personal History:
  - Currently on clopidogrel therapy, or
  - Use of clopidogrel therapy is being proposed for patient at moderate to high risk for poor outcome.

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No No No

VA, NC, SC, WV


81225 CYP2C19 GENE COM VARIANTS
No No No
81226 CYP2D6 GENE COM VARIANTS
No No Yes

See LCD jurisdictions that refer to MolDX.

LCD: MolDX (http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx~MolDx~Browse~By~Topic~General~9BM LRK6738?open&navmenu=Browse^By^Topic|||)

81225 CYP2C19 GENE COM VARIANTS
No No N/A
81226 CYP2D6 GENE COM VARIANTS
No No N/A

References

CYP2C9 & VKORC1 for Warfarin Metabolism

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<td>VKORC1 common variant analysis</td>
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Click here for applicable Medicare NCD/LCD information

Description

Coumadin (warfarin) is used to lower the risk for a thromboembolic event. Warfarin dosing can be challenging as too much warfarin can cause bleeding, and too little warfarin can be associated with a thromboembolic event. Approximately 31 million warfarin prescriptions were dispensed in 2004.1 Bleeding from warfarin use is a common adverse event and can cause substantial morbidity and mortality.1

While warfarin is effective in reducing thrombotic events, it is also associated with 800 reports to the FDA of adverse drug events leading to an ER visit each year.2 The difficulty in dosing warfarin has resulted in a monitoring system called International Normalized Ratio (INR) monitoring system. Dosing is typically adjusted to maintain the INR from 2.0-3.5 depending on the clinical indication. When initiating warfarin, care must be taken to get levels within a therapeutic range and there is a highly variable response between individuals. Reasons for this variability include drug-drug interactions, environmental factors including diet, alcohol consumption and smoking, as well as genetic factors. Genetic factors can explain approximately 40% of warfarin dosing variability.2-4

Genetic variability of warfarin dosing has been associated with polymorphisms in genes that encode the enzymes that metabolize warfarin. Metabolism of warfarin can result in two different clinical scenarios: warfarin resistance and warfarin sensitivity. Warfarin resistance is thought to be infrequent, causing a person to need an increased dose of warfarin to maintain appropriate INR levels. The more common situation is warfarin sensitivity, where an individual requires decreased levels of dosing.

It has been suggested that analysis of multiple single nucleotide polymorphisms (SNPs) in the genes VKORC1 and CYP2C9 could shorten the amount of time for stable dosing and minimize adverse events.5 Genetic testing in two genes - vitamin K epoxide reductase complex 1 gene (VKORC1) and cytochrome P450, family 2, subfamily C, polypeptide 9 (CYP2C9) - are available to help determine dosing levels. Warfarin resistance is a result of heterozygote mutations in VKORC1 and leads to increased warfarin requirements. Two alleles within the VKORC1 gene have been associated with warfarin resistance in the non-Hispanic Caucasian population, and are labeled A and B. BB alleles are wild type, and tend to need higher warfarin doses, and are seen in 35% of non-Hispanic Caucasians. Alleles AB and AA are seen in 47% and 18% of non-Hispanic Caucasians.

The CYP2C9 allele is thought to be the predominant cause of the variation of warfarin dosing.6 There are approximately 37 alleles reported in the CYP complex, however many do not have a functional impact. Two alleles, *2 and *3 (CYP2C9*2 and CYP2C9*3) are linked to a slower metabolism of warfarin, thereby needing an increase in warfarin dose. These alleles are found in approximately 12.2% and 7.9%, respectively, of the European Caucasian population.4 Other variants, *4, *5, and *6 are seen in the Asian and African American populations, but typically around a <1% incidence.7 Diagnosis of these alleles can
occur through sequence analysis of the CYP2C9 and VKORC1 genes. Mutation analysis detects virtually 100% of alleles.²

In 2006, the U.S. Food and Drug Administration (FDA) issued a black box warning for warfarin. This was updated in February 2010 to inform physicians of the variations within two known genes that may require an adjustment of the initial dose of the drug. However, the FDA did not guide physicians as to how initial doses should be changed, due to a lack of supportive clinical evidence.

Testing algorithms have been suggested by several studies;⁵,⁶,⁸-¹² however, their general predictive utility is uncertain. In 2008, two professional groups – the American College of Medical Genetics and Genomics (ACMG)⁶ and The American College of Chest Physicians¹³ (ACCP) indicated that they did not endorse pharmacogenetic testing for warfarin. The ACMG indicated that they did not recommend routine testing for variants in the CYP2C9 and the VKORC1 genes, and the ACCP called for more studies looking into the benefits of testing.

A Rapid-ACCE review of CYP2C9 and VKORC1 indicated several gaps in knowledge that needed further study.² These included which variants should be included in a testing panel, a lack of data from external proficiency testing, lack of validated dosing algorithm, evidence of clinical utility, reliable economic analysis and/or methods to address ELSI implications.

As a result of the above guidelines, genetic testing for warfarin metabolism is not considered medically necessary until a validated dosing algorithm is available, evidence of clinical utility has been proven, and the variants for a testing panel have been decided upon.

Criteria

CYP2C9 Common Variant Testing

Genetic testing is not approved for CYP2C9 common variant testing because it is currently considered experimental, investigational or is unproven.

VKORC1 Common Variant Testing

Genetic testing is not approved for VKORC1 common variant testing because it is currently considered experimental, investigational or is unproven.

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### References


CYP2D6 for Tamoxifen Metabolism

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<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism)</td>
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Description

Approximately 192,000 women are diagnosed with breast cancer each year, of these over 40,000 will die from the disease.1 In the US, women have a 12.2% risk for developing breast cancer.2 The majority of breast cancer tumors (about 80%) express estrogen or progesterone receptor (ER+ or PR+) and therefore are eligible for endocrine therapy. Tamoxifen is the standard of care for premenopausal women with ER+ or PR+ breast cancer and a valid option for treating post-menopausal women. Pre-menopausal women can take tamoxifen for 5 years post cancer which ultimately reduces the recurrence of breast cancer by up to half and mortality by approximately 30%.3 However, a substantial number of tamoxifen-treated patients relapse after surgery and treatment, while others remain disease-free. To be effective, tamoxifen must be metabolized to endoxifin. Over 75 reduced activity alleles have been detected that vary in ability to convert tamoxifen, many of which reduce or eliminate the enzyme function.4

Genetic testing in the gene cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6) is available for multiple single nucleotide polymorphisms (SNPs), deletions, or duplications which may help determine dosing levels. A combination of wild-type alleles (*1, *2, or *31) and either reduced function (*9, *10, *17, *29, or *41) or non-functional (*3, *4, *5, or *6) alleles can manifest into three different phenotypes: extensive metabolizer (EM), intermediate metabolizer (IM) or poor metabolizer (PM). Duplication of a SNP can increase the metabolic function and result in an ultra-metabolizer (UM). It has been suggested that analysis of SNPs in CYP2D6 could identify dosing levels and minimize adverse events.

Most people are extensive metabolizers, meaning that two wild-type alleles with normal CYP2D6 activity levels result in therapeutic endoxifin blood concentrations. Studies indicate that about 46% of the population are extensive metabolizers (defined as having 2 functional CYP2D6 alleles), 48% are intermediate metabolizers (at least one reduced function CYP2D6 allele), and 6% are poor metabolizers (2 nonfunctional CYP2D6 alleles).5,6 Ultra-metabolizers (UM) are seen in approximately 1% of the population. Ultimately, patients with one or more reduced or non-functional alleles do not adequately metabolize tamoxifen and therefore do not respond as well to the drug as extensive metabolizers. In comparison, patients with a duplicated or an increased function allele will metabolize tamoxifen more quickly.

Testing women with non-metastatic breast cancer to predict their response to tamoxifen therapy may inform decisions regarding choice of alternative treatment strategies including chemotherapy or the use of aromatase inhibitors (for post-menopausal women in particular). A recent study investigated the clinical outcomes of an individual’s tamoxifen metabolizing status with their risk for breast cancer recurrence and found that PMs were almost twice as likely to experience breast cancer recurrence than EMs. UMs were not included in this study. Poor, intermediate, and extensive metabolizers had recurrence rates of 29%, 21%, and 15%, respectively, after 9 years follow-up.5 Furthermore, in two studies, African-American women were found to have an increased risk of a PM allele over Caucasian women.6,7 This may, in part, explain the worse outcomes of treatment of breast cancer for premenopausal African-American women.
Breast cancer recurrence risks may differ depending on an individual’s genetic variation, as studies have shown that poor and intermediate metabolizers have significantly lower blood concentrations of tamoxifen’s active metabolite and significantly worse clinical outcomes than extensive metabolizers.\textsuperscript{5,6} One study found that increasing the level of tamoxifen taken by women with reduced or non-functional alleles from 20mg to 40mg will increase the endoxifen blood concentrations to therapeutic levels.\textsuperscript{6} This suggests that by increasing the blood concentration of endoxifen, women taking tamoxifen will increase the benefit of tamoxifen, reducing their risk for breast cancer recurrence to that of women with wild-type alleles.

A 2009 review examined studies and outcomes of women taking tamoxifen with \textit{CYP2D6}-genotypes.\textsuperscript{9} Based on the studies published, this review suggests that it is premature to recommend and act upon pharmacogenetic testing for \textit{CYP2D6}. Additionally, the American Society of Clinical Oncology’s (ASCO) clinical practice update on the use of pharmacogenetic testing for breast cancer reduction indicates that there is not enough evidence to recommend testing \textit{CYP2D6} in the preventive setting.\textsuperscript{10} In 2010, the Agency for Healthcare Research and Quality (AHRQ), Evidence Report/Technology Assessment investigated the analytic validity of SNP testing for \textit{CYP2D6} alleles and agreed with ASCO’s guidelines.\textsuperscript{11} This report found 1) large between-study variability in classifying genotypes to extensive, intermediate or slow metabolizers, 2) most studies evaluated surrogate endpoints, such as disease- or recurrence free survival but their results were inconsistent in direction and formal statistical significance, 3) a few studies evaluated overall survival, but did not demonstrate any significant differences in overall survival by \textit{CYP2D6} status, and 4) most reviewed studies had methodological shortcomings. In addition, a literature review conducted in 2010 found that there were no clinical trials performed that evaluated the net benefit of testing versus not testing in improving health outcomes and were unable to identify any modeling analysis that compared the expected benefits and harms of patient management strategies that are informed by \textit{CYP2D6} testing versus patient management strategies that are not informed by such testing.\textsuperscript{4}

As a result of the above guidelines and recommendations, genetic testing for \textit{CYP2D6} is not considered medically necessary until a validated dosing algorithm is available, evidence of clinical utility has been proven, and the variants for a testing panel have been decided upon.

\textbf{Criteria}

Genetic testing is \textit{not} approved for \textit{CYP2D6} because it is currently considered experimental, investigational or is unproven.

\textbf{References}

11. Terasawa T, Dahabreh IJ, Castaldi PD, TA. T. Systematic Reviews on Selected Pharmacogenetic Tests for Cancer Treatment: CYP2D6 for Tamoxifen in Breast Cancer, KRAS for anti-EGFR antibodies in Colorectal Cancer, and BCR-ABL1 for Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia Project ID: GEN609.
Cystic Fibrosis

Cystic Fibrosis (CF) is a relatively common genetic condition that is found in approximately 1 in 2500 northern European Caucasians and in varying frequencies in other populations. Classic cystic fibrosis is characterized by chronic lower airway disease, gastrointestinal abnormalities, pancreatic insufficiency, male infertility, and salt-loss. Clinically, CF is a variable disease usually diagnosed in childhood based on clinical characteristics and sweat chloride testing. However, approximately 15% of individuals with a milder course of CF symptoms may not be diagnosed until adolescence or adulthood. The life expectancy of patients with CF is reduced as a result of chronic lung disease and pancreatic insufficiency. Aggressive treatment of lung disease and infections has increased the life expectancy from 5 years in the 1960s to 36-37 years presently. Individuals with pancreatic sufficiency have a life expectancy of approximately 56 years.

CF is diagnosed through immunoreactive trypsinogen (IRT) assays, sweat chloride testing, transepithelial nasal potential difference (NPD) and genetic testing. Newborn screening using IRT has been implemented in several states in the US. Newborns with elevated IRT levels are referred for sweat chloride testing or molecular genetic testing. Sweat chloride testing is performed on individuals who exhibit physical symptoms of CF or infants who test positive on newborn screening. Individuals who have elevated chloride levels reflex to genetic testing for CFTR mutations. NPD testing is typically performed on individuals who have tested positive for CF on the sweat chloride testing but are not found to have identifiable CFTR mutations.

Non-classic presentations of CF have also been described. While these conditions do not meet the diagnostic criteria for classic CF, they are caused by mutations in the CFTR gene. These related disorders include congenital absence of the vas deferens (CAVD), bronchiectasis, chronic sinusitis, nasal polyps, and acute or recurrent pancreatitis. The American Society for Reproductive Medicine and the Society for Male Reproduction and Urology (2008) published consensus-based guidelines that recommend cystic fibrosis testing for men with CAVD and their reproductive partners.

CF is an autosomal recessive disorder with a carrier frequency of about 1 in 28 for northern Europeans and Ashkenazi Jews and generally lower carrier frequencies in most other groups of different ethnic or geographic origin. For autosomal recessive conditions, the parents of an affected child are obligate carriers.
(definite) carriers of at least one CFTR mutation, and siblings of an affected individual have a 50% chance of being a carrier, and a 25% chance of being affected with CF.\(^1\)

In 1997, the National Institute of Health Consensus Development Conference published a statement that recommended population screening for individuals with a positive family history of CF, partners of known carriers of CF, and to couples planning a pregnancy or seeking prenatal care.\(^6\) Currently, there are over 1900 novel CFTR mutations that result in symptomatic CF.\(^7\) In 2001, the American College of Medical Genetics and Genomics (ACMG) and the American College of Obstetrics and Gynecology (ACOG) introduced evidence-based guidelines that recommend testing individuals who are pregnant or planning a pregnancy for specific CFTR mutations using a defined mutation panel. The ACMG updated the panel of mutations in 2004. Currently, the standard panel consists of 23 common CF mutations for carrier screening in all ethnic groups.\(^8\) The mutations chosen for the panel contain those with a prevalence >0.1% in the CF population.\(^8\) The ACOG Committee on Genetics published updated guidelines in 2011.\(^9\)

Many laboratories offer expanded mutation panels beyond the standard 23 mutation panel and/or full CFTR gene sequencing. These expanded panels may be clinically indicated in certain circumstances. ACOG guidelines state that expanded panels may be of benefit for individuals whose reproductive partner has a diagnosis of CF or has CAVD. ACOG guidelines also state that CF gene sequencing should be used as a reflex test (when the standard mutation panel is negative) for individuals with a diagnosis of CF, with a family history of CF with an unknown mutation, males with CAVD, and newborns with a positive newborn screening result.\(^9\)

The Ashkenazi Jewish population is at a higher risk for carrying several other autosomal recessive conditions including: Tay Sachs Disease, Gaucher Disease, Canavan Disease, Familial Dysautonomia, Niemann-Pick Type A, Bloom Syndrome, Fanconi Anemia and Mucolipidosis IV. While Cystic Fibrosis is not seen more frequently in the Ashkenazi Jewish population, there is a higher detection rate in this population as most carriers test positive for one of three founder mutations. At present, many laboratories offer tests for multiple conditions as a panel for individuals of Ashkenazi Jewish descent. This can be practical from a convenience and cost perspective. However, an individual should be consented for each condition in the panel. If an individual does not consent to being tested for a particular condition, then each test should be ordered individually.\(^12\),\(^13\) In addition, if CF testing has been performed alone or as part of a panel previously, it should not be repeated.

Evidence and Guidelines

- ACOG committee opinion “Update on Carrier Screening for Cystic Fibrosis” (2011, 2005)\(^9\),\(^10\)
- Cystic Fibrosis Foundation (2008) Guidelines for Diagnosis of Cystic Fibrosis in Newborns through Older Adults: Cystic Fibrosis Foundation Consensus Report\(^11\)
- Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel\(^8\)

As a result of the above guidelines, CareCore has determined that genetic testing should be approved to confirm a diagnosis in anyone who meets clinical criteria for Cystic Fibrosis yet cannot be diagnosed by sweat chloride analysis. Additionally, genetic testing should be approved to determine carrier status in at
risk relatives with a known genetic mutation, individuals considering a pregnancy or currently pregnant, partners of known carriers and individuals of Ashkenazi Jewish descent. Individuals who have a family member with a known CF mutation(s) should be tested for that/those mutation(s). Carrier screening should consist of the 23 mutation panel approved by the ACMG. Extended panel testing through gene sequencing or duplication/deletion analysis is not approved unless under prior authorization. Women and their partners who are found to be carriers of a CFTR mutation, or are affected by CF, are eligible for prenatal testing to determine the CF status of the fetus. If mutations are known, prenatal testing can be performed by either a CVS or amniocentesis.

Criteria
Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

**CFTR Standard Panel Testing**

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing for CFTR mutation(s), AND
- Diagnostic Testing for Symptomatic Individuals:
  - Individuals with a intermediate range/equivocal sweat chloride test (30-55mmol/L in infants, or 40-59mmol/L after 6 months of age), or
  - Individuals with a negative sweat chloride test when
  - Symptoms of CF are present, or
  - Idiopathic chronic (acute recurrent) pancreatitis present with non-focal workup, or
  - Infants with meconium ileus or other symptoms indicative of CF and are too young to produce adequate volumes of sweat for sweat chloride test, or
  - Infants with an elevated IRT value on newborn screening, or
  - Males with oligospermia/azoospermia/congenital absence of vas deferens (CAVD), OR
- Carrier Screening:
  - Be of reproductive age, and
  - Have potential and intention to reproduce, or
  - Have reproductive partner with family history of CF, or
  - Have reproductive partner with CAVD, or
  - Currently pregnant, OR
- Embryos or At-Risk Fetuses:
  - Either biological parent has a diagnosis of CF, or
  - Family history of CF is present, or
  - Both parents are carriers of CF mutations, or
  - Echogenic bowel has been identified on ultrasound in a fetus, OR
- Rendering laboratory is a qualified provider of service per the Health Plan policy.
CFTR Family Mutation(s) Testing

- Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy)\(^{14}\), AND
- Previous Testing:
  o No previous genetic testing for known CFTR family mutation(s), or
  o Previous CFTR panel testing was not inclusive of known family mutation, AND
- Carrier Screening:
  o Family CFTR mutation(s) in known biologic relative, OR
- Embryos or At-Risk Fetuses:
  o Either biological parent is a known carrier of a CFTR mutation, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CFTR Complete Gene Sequencing\(^{†}\)

- Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy)\(^ {14}\), AND
- Previous Genetic Testing:
  o Previous CFTR Standard Panel was negative (no mutation found) or only one mutation was found, AND
- Diagnostic Testing for Symptomatic Individuals:
  o Individuals with a negative or equivocal sweat chloride test, and
    ▪ Unexplained COPD or bronchiectasis with unexplained chronic or recurrent sinusitis and abnormal pulmonary function tests (PFTs), or
    ▪ Idiopathic chronic (acute recurrent) pancreatitis is present, or
  o Infants with meconium ileus or other symptoms indicative of CF and are too young to produce adequate volumes of sweat for sweat chloride test, or
  o Infants with an elevated IRT value on newborn screening and a negative 23 mutation panel, OR
- Carrier Screening
  o An individual with a family history of CF with an unknown mutation, or
  o An individual whose reproductive partner is a known CF carrier, has a diagnosis of CF, or has a diagnosis of CAVD, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

\(^{†}\)Lab Testing Restrictions: Previous CFTR Standard Panel was negative

CFTR Deletion/Duplication Testing\(^{†}\)

- Genetic Counseling
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing:
  o No previous CFTR deletion/duplication testing, and
  o Previous CFTR Gene Sequencing was negative (no mutation found) or only one mutation was found, and
  o No known familial mutation, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy

†Lab Testing Restrictions: Previous CFTR Gene Sequencing was negative

**CFTR Intron 8 Poly T Analysis†**

• Genetic Counseling
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing:
  o No previous CFTR intron 8 poly T testing, AND
• Diagnostic testing:
  o Diagnosis of male infertility (congenital absence of vas deferens [CAVD], obstructive azoosperma), or
  o Diagnosis of non-classic CF, OR
• Carrier testing†:
  o CFTR mutation analysis performed and R117H mutation detected
• Rendering laboratory is a qualified provider of service per the Health Plan policy

†Lab Testing Restrictions: R117H mutation previously detected by CFTR analysis

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VA, NC, SC, WV


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See LCD jurisdictions that refer to MolDX.


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| 81224 CFTR GENE INTRON POLY T | No | No | N/A |

References

7. Cystic Fibrosis Centre at the Hospital for Sick Children in Toronto. [http://www.sickkids.ca/Centres/Cystic-Fibrosis-Centre/](http://www.sickkids.ca/Centres/Cystic-Fibrosis-Centre/)


Dentatorubral-Pallidoluysian Atrophy (DRPLA)

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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specific sequence to be followed or additional information is required and must be supplied by the lab performing procedure(s) for full claim payment.

Description

Dentatorubral-pallidoluysian atrophy (DRPLA) is a progressive neurologic disorder which typically presents in adults (individuals over ~age 20) with ataxia, choreoathetosis, and dementia or character changes (known as the non-progressive myoclonic epilepsy phenotype or non-PME phenotype). As the disease progresses, most individuals develop all findings. In individuals under ~age 20, DRPLA typically manifests with progressive intellectual deterioration, behavior changes, ataxia, myoclonus, and seizures (known as the progressive myoclonic epilepsy phenotype or PME phenotype). Age of onset ranges from one year of age to 62 years of age; the mean age of onset is 30 years of age.¹ Neuropathology demonstrates degeneration of the dentatorubral and pallidoluysian systems.² In addition, white matter lesions have been described.¹ DRPLA is also known as Myoclonic Epilepsy with Choreoathetosis; Naito-Oyanagi Disease; Haw River Syndrome; Ataxia, Chorea, Seizures, and Dementia.³ ⁴ Its prevalence is estimated to be about 0.48 in 100,000 in the Japanese population based on a study conducted by Tsjuji et al in 2008.⁵

The diagnosis of DRPLA is based on presenting findings, family history, and the results of molecular genetic testing demonstrating an expansion of the CAG trinucleotide/polyglutamine tract in ATN1.¹ Normal alleles typically have a repeat length of 6 to 35; individuals with DRPLA have a full penetrance allele with repeat length > 48 repeats, usually 48-93.¹ ⁶ So-called ‘mutable normal’ alleles may exist, i.e., alleles with repeats between 36 and 47. Mutable normal alleles do not result in symptoms for the individual, but they are unstable and may increase in size when transmitted to offspring.¹

DRPLA is inherited in an autosomal dominant manner. Males and females are affected. Each individual with DRPLA has a 50% chance of passing the ATN1 mutation (which is an expanded trinucleotide (CAG) repeat) to each of his/her offspring. Most individuals with DRPLA have inherited the mutation from a parent.

DRPLA likely has an exceedingly small incidence of de novo mutations because as part of its mechanism of occurrence, it has a method to remain in the population. Unaffected persons with mutable normal or intermediate alleles may pass this allele to offspring and the allele may undergo intergenerational expansion to a disease-causing range. Thus, most (or all) cases of molecularly confirmed DRPLA that appear to be the result of a new mutation will more likely be the result of inheritance of a repeat that expanded in size from parent to child. The parent may not have had signs of DRPLA because the number of repeats he or she had were below the ‘threshold’ for manifesting symptoms (‘mutable normal’ or ‘intermediate’ alleles) or the number of repeats was within the disease-causing range, but small in number thus the parent with the abnormal allele has not yet developed symptoms.
The age of onset and clinical presentation is indirectly correlated with the size of the expansion. On average, individuals with large expansions have earlier onset (and the PME phenotype) than those individuals with a smaller number of repeats. Shimojo et al (2001) reported an individual with severe infantile onset. This child was found to have a CAG expansion of 90-93 repeats. Sato et al (1995) reported a person who was homozygous for the CAG expansion in ATN1 (i.e., both copies of ATN1 had a CAG expansion) who was more severely affected with earlier onset than individuals with only one expanded allele of the same size. The size of the trinucleotide repeats inherited by a child depends upon the size of the repeat and gender of the transmitting parent. When the expansion is inherited from the father, intergenerational increase in size of the expansion tends to be larger than when the disease-causing allele is inherited from the mother. As a result, individuals who inherit the mutation from their father tend to have onset of disease 26-29 years earlier than their affected parent; when inheritance is from the mother, the onset of disease is about 14-15 years earlier.

Although initially thought to be a disorder of the Japanese population, DRPLA has been diagnosed in individuals from a variety of non-Japanese backgrounds. Wardle et al (2009) reported a systematic literature review which identified 183 individuals with DRPLA from 27 non-Japanese families. To be included in the study at least one affected member of each family had the diagnosis of DRPLA confirmed by molecular genetic testing. In the non-Japanese group, the mean age of onset was 31 years (range 1-67), similar to mean age of onset and range for Japanese patients. Repeat length instability observed in Japanese patients was similar to that observed in non-Japanese individuals.

In 1994, a large African-American family was reported with an autosomal dominant neurodegenerative disorder with findings similar to those found in individuals with DRPLA. Named Haw River syndrome, affected individuals in this family had the onset of symptoms between the ages of 15 and 30. Typically, the first symptoms were ataxia followed by personality changes. Chorea and seizures developed later, followed by dementia. Most individuals with Haw River syndrome have developed seizures, whereas only about half of individuals with DRPLA who are older than 20 years develop seizures. All affected individuals with Haw River syndrome have expanded CAG repeats ranging from 63 to 68 repeats.

Initially individuals with DRPLA were classified into three clinical phenotypes: the sporadic ataxo-choreoathetoid type, familial pseudo-Huntington type, and the myoclonic epilepsy type. The ‘familial pseudo-Huntington type’ now known as the adult non-PME phenotype and the ‘myoclonic epilepsy type’, now known as the PME-phenotype are diagnosed in individuals who have a CAG trinucleotide expansion in ATN1. Individuals with the so-called ‘sporadic DRPLA’ do not have a CAG trinucleotide expansion in ATN1. They may have a different mutation in ATN1 or a mutation in a different, as yet unidentified, gene. Cases of DRPLA without the CAG trinucleotide expansion in ATN1 are not included in this document.

A diagnosis of DRPLA requires molecular genetic testing to identify the number of CAG trinucleotide/polyglutamine repeats in ATN1. Once the diagnosis is confirmed with genetic testing, pre-symptomatic/predictive testing, prenatal diagnosis, and preimplantation genetic diagnosis are available to at-risk family members. Although the size of the trinucleotide repeat is inversely correlated with the age of onset, the number of repeats cannot be used for specific prediction of symptoms or age of onset in an asymptomatic person. Repeat length is estimated to account for 50-68% of the variability in age of onset, the other contributing factors are not known.

Based on the evidence, CareCore National has determined that individuals ~20 years of age and older can be considered for diagnostic genetic testing if they have at least two of the typical findings of ataxia,
choreoathetosis, and dementia or character changes. Individuals younger than 20 years of age are considered for diagnostic genetic testing if they have at least two of the findings associated with the PME phenotype: myoclonus, ataxia, seizures, or progressive intellectual deterioration/behavior changes. An individual who has a first degree relative who meets the above criteria but in whom the mutation status is unknown, an ATN1 CAG trinucleotide expansion has been detected, or is of Japanese or Haw River family descent need only have one of the findings above.

After examination by a geneticist or physician familiar with DRPLA and after comprehensive genetic counseling by a medical geneticist and/or genetic counselor, genetic testing is recommended for individuals who have a 1st or 2nd degree relative with an identified ATN1 CAG trinucleotide repeat. Prenatal or preimplantation genetic diagnosis is available to at risk offspring when one biologic parent has been identified to have an ATN1 CAG trinucleotide repeat. Prior genetic counseling by a medical geneticist and/or genetic counselor at the prenatal or PGD facility is required. Because pre-symptomatic/predictive testing, prenatal diagnosis, and/or preimplantation genetic diagnosis require molecular genetic confirmation of the diagnosis, testing of an un-covered family may be necessary in order to provide at-risk family members with services.

Criteria

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

- Clinical Consultation & Genetic Counseling:
  - Examination by a geneticist or physician familiar with hereditary neurological disease and
  - Pre and post-test counseling by a medical geneticist, and/or genetic counselor, or specialst familiar with hereditary neurological disease, AND

- Previous Testing:
  - No previous ATN1 testing for DRPLA, AND

- Diagnostic Testing for Symptomatic Individuals:
  - < 20 years of age and 2 or more of the following:
    - Ataxia
    - Myoclonus
    - Seizures
    - Progressive intellectual deterioration/behavior changes
    - Affected 1st degree biologic relative or Japanese/Haw River descent, OR
  - ≥ 20 years of age and 2 or more of the following:
    - Ataxia
    - Choreoathetosis
    - Affected 1st degree biologic relative or Japanese/Haw River descent, OR

- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - ATN1 CAG trinucleotide expansion detected in 1st degree biologic relative, or
  - Suspected DRPLA in a deceased 1st, 2nd, or 3rd degree biologic relative who was not genetically diagnosed
References

1. DRPLA. University of Washington. [http://www.genetests.org]
DPD Deficiency Testing

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81400 No No

* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Click here for applicable Medicare NCD/LCD information

Description

5-fluorouracil (5-FU) is an injectable chemotherapy agent commonly used in the treatment of colorectal, gastric, pancreatic, head, neck, breast, ovarian, and cervical cancers. 5-FU is also available in a topical formulation and orally in the form of a pro-drug (capecitabine). The metabolism of 5-FU is primarily dependent on the enzyme dihydropyrimidine dehydrogenase (DPD) which converts 5-FU to a less toxic form. The dihydropyrimidine dehydrogenase (DPYD) gene encodes the DPD enzyme. Individuals who have low DPD enzyme levels due to genetic variants in DPYD are prone to experiencing unexpected, severe toxicity (e.g., stomatitis, diarrhea, neutropenia, and neurotoxicity). Current FDA labeling warns of a link between decreased levels of DPD and increased, potentially fatal toxic effects of 5-FU. Drugs containing 5-FU are contraindicated in individuals with DPD deficiency.

Criteria

DPD deficiency testing by DPYD IVS14+1G>A variant analysis is indicated in individuals considering or currently on therapy with any 5-FU containing drug:

- 5-fluorouracil (Fluorouracil®, Adrucil®)
- Capecitabine (Xeloda®)
- Fluorouracil topical formulations (Carac®, Efudex®, Fluoroplex®)

NCD/LCD Jurisdiction and CPT Codes

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DPD Deficiency Testing

See LCD jurisdictions that refer to MolDX.

LCD: MolIDX

(http://www.palmettogba.com/palmetto/MolDX/DocsCat/MolDX%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse*By*Topic|]])

81401 MOPATH PROCEDURE LEVEL 2
References


## Duchenne/Becker Muscular Dystrophy

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[Click here for applicable Medicare NCD/LCD information](#)

### Description

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are part of the spectrum of dystrophinopathies caused by mutation in DMD, the gene encoding dystrophin. The phenotype of asymptomatic increase in serum concentration of creatine phosphokinase (CK), muscle cramps with myoglobinuria, and isolated quadriceps myopathy is associated with the mild end of the spectrum of phenotypes associated with DMD mutations. The severe end of the spectrum includes Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD), conditions in which skeletal muscle is affected and DMD-related cardiomyopathy, a condition in which cardiac muscle is primarily affected (4). This policy addresses testing for individuals with known or suspected Duchenne or Becker muscular dystrophy. In their recently published study, Mah et al. (2011) (7) estimated the prevalence of dystrophinopathies in Canada to be 1.5/10,000 males which is consistent with a 2007 study done in the United States which found a prevalence of 1.3-1.8 per 10,000 males aged 5–24 years (3). Hermans et al. (2010) stated that the incidence of Duchenne muscular dystrophy to be 1 in 3500 males and Becker muscular dystrophy to be about 1 in 18,450 males (5).

DMD, the gene encoding dystrophin, is the largest gene described in humans. It spans more than 2.5 million base pairs of genomic DNA and comprises 0.1% of the human genome. The majority of the gene is comprised of introns; there are 86 exons (including seven promoters linked to unique first exons). The messenger RNA transcribed from DMD is primarily expressed in skeletal and cardiac muscle and a small amount in brain (9). Almost 2300 mutations are recorded in HGMD professional version (10). Mutation types include deletion of the entire gene, deletion or duplication of single or multiple exons, small deletions, insertions and single base alterations. In general, mutations that lead to lack of dystrophin expression cause Duchenne MD; mutations that lead to abnormal quantity or quality of dystrophin lead to Becker MD (4).

Duchenne muscular dystrophy (DMD) is characterized by progressive symmetrical muscular weakness, proximal greater than distal, often associated with calf hypertrophy and presenting in males before age five years. Many boys with DMD are wheelchair dependent by age 13 years (4). Weakness of leg, pelvic and shoulder girdle muscles starting in early childhood is typical (5). Serum CK concentrations are 10X normal in boys with DMD although the levels decrease with age. Immunohistochemistry of muscle biopsy from individuals with DMD demonstrates complete or almost complete absence of the dystrophin protein (4).
Delayed milestones, including delays in sitting and standing independently are a typical early childhood presentation for males. The mean age of walking is approximately 18 months (range 12-24 months). The first symptoms of DMD as identified by parents are typically: general motor delays (42%); gait problems, (30%); delay in walking (20%); learning difficulties (5%); and speech problems (3%). Proximal weakness causes a waddling gait and difficulty climbing; boys use the Gower maneuver to rise from a supine position, using the arms to supplement weak pelvic girdle muscles. The calf muscles are hypertrophic and firm to palpation. Boys with DMD typically have some degree of non-progressive cognitive impairment; over time, a specific cognitive profile of boys with DMD has emerged, demonstrating deficits in working memory and executive function (4).

Uncommon presentations of DMD include (1) affected girls, explained by non-random X chromosome inactivation, either by chance or as the result of an X:autosome translocation or other X chromosome abnormality and (2) boys with additional findings of retinitis pigmentosa, chronic granulomatous disease, and McLeod red cell phenotype who have a contiguous gene deletion syndrome. Chromosome analysis is warranted for individuals with these presentations (4). In a study of 129 DMD carriers, Hoogerwaard et al. 1999 (6) found that 22% had clinical manifestations including muscle weakness and dilated cardiomyopathy. In addition, 18% had left ventricular dilation. Because of the increased risk of cardiac disease in carriers of DMD mutations, the American Academy of Pediatrics Section on Cardiology and Cardiac Surgery has published recommendations for management of these women (2).

Becker muscular dystrophy (BMD) is also characterized by progressive symmetrical muscle weakness and atrophy with proximal greater than distal and often associated with calf hypertrophy. However, BMD has a later-onset skeletal muscle weakness, mean age of onset is about 11 years (range: 3-21 years) (5); individuals remain ambulatory into their 20s. Additional presentations may include weakness of quadriceps femoris as the only sign and activity-induced cramping. Preservation of neck flexor muscle strength in individuals with BMD differentiates it from DMD. In addition, wheel chair dependency, if present, typically does not occur until after age 16 in males with BMD. Flexion contractures of the elbows may also occur late in the course of the disease. CK concentrations are 5X normal in boys with BMD although the levels decrease with age. Cognitive impairment is not as common or as severe as in DMD (4). Cardiac involvement however is more common and severe than in individuals with DMD accounting for the cause of death in approximately 50% [5]. Cardiac involvement is present in approximately 90% of individuals with DMD/BMD; however, cardiac involvement is the cause of death in only 20% of individuals with DMD and 50% of those with BMD (5).

DMD and BMD phenotypes are correlated with the degree of expression of dystrophin which can be determined with some accuracy based on specific mutations. Large deletions and mutations that result in absence of dystrophin expression result in DMD, while BMD results when the mutation in DMD results in some dystrophin production (4). Molecular genetic testing of symptomatic individuals with an elevated CK level for DMD or BMD begins with deletion/duplication analysis using one of a number of specific methods (e.g., MLPA, array CGH etc.). Approximately 50-65% of individuals with Duchenne dystrophy and about 70% of males with Becker dystrophy have deletions of one or more exons or of the entire DMD gene. Duplication of one or more exons occurs in about 5-10% of individuals with Duchenne or Becker MD. Therefore, deletion/duplication analysis should be performed first (4, 7). If a deletion or duplication is not identified in a symptomatic individual, sequence analysis/mutation scanning is performed. Twenty-five to 35% of individuals with Duchenne or Becker MD have mutations identifiable by sequence analysis (4, 7).
Almost all individuals with Duchenne/Becker MD have an identifiable DMD mutation. The identification of a DMD mutation confirms the diagnosis. Muscle biopsy, with its associated medical risks and expense, is usually not required for diagnosis (4). Muscle biopsy can help distinguish Becker MD from Duchenne MD in young boys without a family history; however, the DMD mutation type is generally thought to be 91% accurate in establishing the specific expected phenotype (1). Muscle biopsy with subsequent immunohistochemistry and/or western blot analysis to detect the absence of or alteration in dystrophin may be indicated for individuals in whom a DMD mutation is not identified (7). However, molecular genetic testing for mutations associated with some forms of limb-girdle muscular dystrophy that have phenotypic overlap with Duchenne/Becker MD may be considered first.

DMD and BMD, caused by mutations in DMD, are inherited in an X-linked manner. Most men with DMD do not reproduce. All daughters of men with BMD will be obligate carriers of their father’s DMD mutation; all sons of men with BMD will not be carriers nor will they be affected. Females who are carriers of a DMD mutation have a 50% chance of passing on the mutation with each pregnancy. Females who inherit the mutation will be carriers; males who inherit the mutation will be affected. Approximately 2/3 of women who have a son with DMD and who have no family history of DMD are carriers. In addition, the incidence of germline mosaicism in mothers is 15%-20%, thus the sibs of affected males are at risk of being affected (if male) or carriers (if female) even when the disease-causing DMD mutation is not detected by molecular genetic testing of the mother leucocytes (4).

Males with DMD mutations are treated with corticosteroid therapy between ages five and 15 years in accordance with the national practice parameters regarding corticosteroid therapy developed by the American Academy of Neurology and the Child Neurology Society. Such therapy has been demonstrated to have a beneficial effect on muscle strength and function in these individuals (8).

Because some treatment to reduce morbidity in individuals with DMD mutations is available (8), molecular genetic testing of affected individuals is appropriate. In addition, carrier testing, pre-symptomatic/predictive testing, prenatal diagnosis, and/or preimplantation genetic diagnosis are best done after molecular genetic confirmation of the diagnosis and identification of the specific mutation in the family. Testing of an uncovered family may be necessary in order to provide at-risk family members with services. Since cardiac surveillance is recommended to female carriers (2) at-risk female relatives should be offered molecular genetic testing even if the family-specific mutation is not known, i.e., in the situation where an affected family member or obligate carrier is unavailable for testing.

New treatments for dystrophinopathies under investigation include (1) nonsense suppression therapy with small molecule drugs (e.g., PTC124 or gentamicin) which attempts to increase ribosomal read through of premature stop codon during translation to result in a modified dystrophin protein and (2) exon-skipping which uses synthetic sequences that correct the reading frame shift by ‘skipping over’ specific exons resulting in an internally truncated protein (7). Knowledge of the specific disease-causing mutation in an individual will be critical to utilizing these treatments.
Criteria

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result in a medical review of the case.

Known DMD Family Mutation Testing

- Clinical Consultation & Genetic Counseling:
  - Examination by a geneticist or physician familiar with hereditary neurological disease and
  - Pre and post-test counseling by a medical geneticist and/or genetic counselor, or a specialist familiar with neurological disease, AND
- Previous Genetic Testing:
  - No previous genetic testing of DMD, AND
- Diagnostic or Predictive Testing and Carrier Screening:
  - DMD mutation identified in 1st, 2nd, or 3rd degree biologic relative(s).

DMD Deletion/Duplication Analysis

- Clinical Consultation & Genetic Counseling:
  - Examination by a geneticist or physician familiar with hereditary neurological disease and
  - Pre and post-test counseling by a medical geneticist and/or genetic counselor, or specialist familiar with hereditary disease, AND
- Previous Testing:
  - No previous DMD genetic testing, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Progressive symmetric muscle weakness (proximal greater than distal), i.e., leg, pelvic and shoulder girdle muscles, and calf hypertrophy, and positive Gower maneuver, or
  - Elevated serum CK concentration, and
  - Progressive symmetric muscle weakness (proximal greater than distal), i.e., leg, pelvic and shoulder girdle muscles, or
  - Calf hypertrophy, or
  - Positive Gower maneuver, or
  - Male gender, or
  - Onset of symptoms by early adulthood (usually by adolescence), or
  - Delayed motor milestones, or
  - Gait problems; waddling gait or
  - Learning difficulties, or
  - Quadriceps weakness; activity-induced cramping, or
  - Family history consistent with X-linked inheritance, OR
- Carrier Screening and Predictive Testing for Presymptomatic/Asymptomatic at Risk Individuals:
  - DMD or BMD diagnosed in 1st or 2nd degree family member and no known mutation at this time, and
  - Family history consistent with X-linked inheritance, OR
**DMD Reflex Full Sequence Analysis†**

- Clinical Consultation & Genetic Counseling:
  - Examination by a geneticist or physician familiar with hereditary neurological disease and
  - Pre and post-test counseling by a medical geneticist and/or genetic counselor, or a
    specialist familiar with neurological disease, AND

- Previous testing:
  - No mutations detected by deletion/duplication analysis in DMD, and
  - No previous full sequencing analysis of DMD

†Lab Testing Restrictions: Testing is authorized after no mutations detected with deletion/duplication analysis.

### NCD/LCD Jurisdiction and CPT Codes

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### References


10. HGMD [https://portal.biobase-international.com/cgi-bin/portal/login.cgi](https://portal.biobase-international.com/cgi-bin/portal/login.cgi) (professional version)

EGFR Mutation Analysis, NSCLC

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**Description**

Erlotinib (Tarceva®) is an oral chemotherapy drug used in the treatment of non-small cell lung cancer (NSCLC). Erlotinib is also a first-line treatment for locally advanced, unresectable or metastatic pancreatic cancer when used in combination with gemcitabine. Tumors with mutations in the epidermal growth factor receptor (EGFR) gene respond better to erlotinib than tumors that lack this mutation. EGFR testing is routinely performed on lung tissue samples. National Comprehensive Cancer Network guidelines for the treatment of non-small cell lung cancer recommend erlotinib for individuals with EGFR positive tumors.

**Criteria**

EGFR mutation testing is indicated in individuals with non-small cell lung cancer prior to initiation of treatment with erlotinib therapy.

**NCD/LCD Jurisdiction and CPT Codes**

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Click here for applicable Medicare NCD/LCD information

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CareCore Laboratory Laboratory Management Criteria V1.0.2015

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400 Buckwalter Place Boulevard, Bluffton, SC 29910 • (800) 918-8924 www.carecorenational.com
81235 EGFR GENE COM VARIANTS | Yes | Yes | No
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See LCD jurisdictions that refer to MolDX.

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81235 EGFR GENE COM VARIANTS | No | No | N/A
81479 UNLISTED MOLECULAR PATHOLOGY | cobas EGFR Mutation Test | Yes | No | N/A

See LCD jurisdictions that refer to MolDX.

**LCD: MolDX** ([link](http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Covered%20Tests~9BGQSN5862?open&navmenu=Browse*By*Topic|||))

81479 UNLISTED MOLECULAR PATHOLOGY | cobas EGFR Mutation Test | Yes | No | N/A

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Factor II (Prothrombin)

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<td>Hereditary hypercoagulability F2 (prothrombin, coagulation factor II) gene analysis, 20210G&gt;A variant.</td>
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Description

- Prothrombin thrombophilia is a genetic disorder that increases one’s risk for developing abnormal blood clots (venous thromboembolism or VTE).¹
- Prothrombin thrombophilia is caused by a genetic change, or mutation, in the F2 gene called G20210A.¹-³
  - The F2 gene produces a protein that helps to initiate the formation of blood clots.¹
  - The prothrombin mutation shifts the F2 gene into overdrive, increasing one’s risk of VTE.¹
  - The prothrombin mutation is one of several mutations linked to an increase risk for blood clotting.²,³
- The formation of abnormal blood clots can lead to conditions like deep vein thrombosis (DVT) and pulmonary embolism.¹,²
- Prothrombin thrombophilia is also linked to an increased risk of miscarriage or other pregnancy complications like preeclampsia, slow fetal growth, and placental abruption.¹,²
- About 2% of Caucasians have at least one prothrombin mutation.¹,²
  - Inheriting one prothrombin mutation increases one’s risk for developing VTE threefold.¹
  - Inheriting two prothrombin mutations increases one’s risk twentyfold.¹
  - Inheriting a prothrombin mutation with other genetic risk factors such as Factor V Leiden also significantly increases the risk for developing VTE.¹
- Definitive diagnosis of prothrombin thrombophilia relies on both clinical and genetic testing.²,³
- Individuals with the prothrombin mutation often have mildly elevated prothrombin levels. These levels can be measured directly in suspected cases of prothrombin thrombophilia.²
  - However, levels vary among individuals and even overlap significantly with the normal range.²
  - Prothrombin levels are therefore not reliable for the diagnosis of prothrombin thrombophilia, and mutation analysis remains the best choice for definitive diagnosis.²
- Mutation analysis looks for the G20210A mutation in the F2 gene, and determines how many copies of that mutation are present.²,³
  - Understanding the number of prothrombin mutations in a suspected case is essential for proper diagnosis, management, and screening.
  - The detection rate for prothrombin mutation analysis is virtually 100%.²,⁴
- An Agency for Health Care Research and Quality supported systematic review (AHRQ, 2009) found that, while mutation analysis is effective at identifying prothrombin mutations, “the
incremental value of testing individuals with VTE for these mutations is uncertain. The literature does not conclusively show that testing individuals with VTE or their family members for FVL or prothrombin G20210A confers other harms or benefits. If testing is done in conjunction with education, it may increase knowledge about risk factors for VTE.\textsuperscript{6,8}

**Criteria**

Consideration for Factor II (prothrombin) G20210A genetic testing for thrombophilia is determined according to guidelines from the American College of Medical Genetics, the College of American Pathology, the National Society of Genetic Counselors, and the American College of Obstetricians and Gynecologists.\textsuperscript{3,6-9}

Testing is indicated in individuals who meet ANY of the following criteria:

- Venous thromboembolism (VTE) at a young age (<50 years); OR
- Recurrent VTE; OR
- Unusual VTE site, such as those involving the hepatic, portal, mesenteric, or cerebral veins; OR
- VTE associated with pregnancy or oral contraceptive use; OR
- VTE associated with hormone replacement therapy, selective estrogen receptor modulators (SERMs), or tamoxifen; OR
- Personal and close family history of VTE; OR
- Unprovoked VTE at any age; OR
- Family history of venous thrombosis at a young age (<50 years); OR
- Women experiencing recurrent pregnancy loss; OR
- Women with a history of other unexplained poor pregnancy outcomes, including severe preeclampsia, placental abruption, fetal growth retardation, and stillbirth; OR
- Family history of either mutation, particularly when results may impact oral contraceptive use or pregnancy management; OR
- Myocardial infarction before age 50, particularly in female smokers

### NCD/LCD Jurisdiction and CPT Codes

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References


Factor V Leiden

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**Description**

Factor V Leiden (FVL) is an inherited condition characterized by an inability to coagulate with protein C, and an increased risk for venous thromboembolism (VTE). While most cases of VTE occur in adulthood, individuals with FVL can have a VTE at a younger age, with some having recurrent VTE by age 30. VTE typically occurs as a deep vein thrombosis (DVT), which most commonly occur in the legs, however they can also occur as a pulmonary embolism (PE; blood clot in the lungs). VTE is a multifactorial condition, usually arising from a combination of genetic, acquired and circumstantial events and risk factors.

Inherited and acquired thrombophilia have also been associated with early miscarriage. Several studies have found that women with a thrombophilia allele were at an approximately 8% risk for miscarriage, as compared to the general population risk of 0.9%. Other pregnancy complications, including preeclampsia, intrauterine growth restriction, and placental abruption have been reported in the literature.

FVL is the most common inherited cause of VTE, seen in approximately 20-25% of individuals with a VTE. FVL is inherited in an incomplete autosomal dominant pattern. The risk for thrombosis depends on whether one or two FVL mutations are present. In a family study, 40% of homozygotes had a VTE by the age of 33 years, compared with 20% of heterozygotes and 8% of unaffected individuals. Population studies suggest approximately 10% of Factor V Leiden heterozygotes develop VTE over their lifetime. The incidence of VTE is 1 per 1000 person years, with the lifetime risk of VTE being higher (25–40%) in heterozygotes from thrombophilic families leading to 50,000 deaths annually. It is estimated that 3–5% of the Caucasian population in the United States is heterozygous and 1% are homozygous for a FVL mutation, making FVL one of the most common tests ordered. The allele is seen more commonly in Sweden and Greece (8-10%) but is rare in Asian, African, and indigenous Australian populations.

One gene, F5, is associated with Factor V Leiden. The 1691G>A (R506Q) mutation in F5 is associated with the FVL phenotype. The presence of symptoms is seen more frequently in homozygotes, and heterozygotes from thrombophilic families. Heterozygotes identified from the general population are at a lower risk of clotting then those from thrombophilic families. This is true even during events that would increase the risk for a DVT or PE.

General consensus is that there is clinical utility for FVL testing, although the guidelines regarding when to test may differ. The decision to test should be determined on the management of the individual person. Once a deleterious mutation has been identified, relatives of affected individuals can be tested. Early detection of at-risk individuals affects medical management in families who have a history of clotting.
Although prenatal genetic testing through amniocentesis or chorionic villus sampling is available to individuals with a known family mutation, it is not often used due to limited clinical utility in the prenatal setting.

As a result of the above guidelines, genetic testing for the \( F5 \ 1691G>A \ (R506Q) \) mutation should be approved to confirm a diagnosis or predisposition in anyone who meets clinical criteria for FVL. Additionally, genetic testing should be approved to determine the carrier status in an at risk relative with a known FVL family mutation.

Once identified as a carrier, the management of individuals with Factor V Leiden depends on the clinical circumstances. The first acute VTE should be treated according to standard guidelines.\(^{17}\)

**Criteria**

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

- **Genetic Counseling**
  - Pre and post-test counseling by a medical geneticist, genetic counselor, or other specialist as deemed by Health Plan policy, AND
- **Previous Genetic Testing:**
  - No previous genetic testing for Factor V Leiden mutation, AND
- **Diagnostic Testing for Symptomatic Individuals:** \(^{1}\)
  - A first unprovoked VTE at any age (especially age <50 years), or
  - A history of recurrent VTE, or
  - Venous thrombosis at unusual sites (e.g., cerebral, mesenteric, hepatic, and portal veins), or
  - VTE during pregnancy or the puerperium, or
  - VTE associated with the use of estrogen contraception or hormone replacement therapy (HRT), or
  - A first VTE with a first-degree family member with VTE before the age of 50 years, or
  - Women with recurrent unexplained first-trimester pregnancy losses with or without second or third trimester pregnancy losses, or
  - Selected women with unexplained severe preeclampsia, placental abruption, or a fetus with severe intrauterine growth restriction, or
  - A first VTE related to the use of tamoxifen or others elective estrogen receptor modulators (SERMs), or
  - Female smokers younger than age 50 with a myocardial infarction or stroke, or
  - Individuals older than age 50 with a first provoked VTE in the absence of malignancy or an intravascular device, or
  - Abnormal results on Activated Protein C (APC) resistance assay, OR
- **Predisposition Testing for Presymptomatic/Asymptomatic Individuals:**
  - Known \( F5 \ 1691G>A \ (R506Q) \) mutation family mutation identified in 1st degree relative(s). (Note: 2nd or 3rd degree relatives may be considered when 1st degree relatives are unavailable or unwilling to be tested), or
- Biologic relative(s) (1st degree) diagnosed with FVL clinically, and no family mutation identified, or
- Women with recurrent unexplained first-trimester pregnancy losses with or without second or third trimester pregnancy losses, or
- Neonates and children with non-catheter related idiopathic VTE or stroke, OR

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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Familial Adenomatous Polyposis (FAP) and Attenuated FAP

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† - Lab procedures require specific sequence to be followed or additional information is required and must be supplied by the lab performing procedure(s) for full claim payment.

Click here for applicable Medicare NCD/LCD information

Description

APC gene mutations cause Familial Adenomatous Polyposis (FAP), Attenuated FAP, Gardner and Turcot syndromes.

- **FAP** is characterized by multiple (>100) colorectal polyps. The development of hundreds to thousands of polyps begins at the average age of 16. If left untreated, individuals with FAP will inevitably develop colorectal cancer by the fourth decade (average age of 39). FAP is also characterized by extracolonic manifestations, including upper gastrointestinal tract polyps (gastric fundus and duodenum), osteomas (Gardner syndrome), thyroid cancer (female preponderance), and hepatoblastoma in children. Epidermoid cysts, mainly in the scalp, and dental anomalies (e.g. unerupted teeth) and jaw tumors also occur. Multiple areas of retinal pigmentation, known as congenital hypertrophy of the retinal pigmented epithelium (CHRPE) are specific in a person with a family history of FAP but are not sensitive for population screening.¹

- **Attenuated FAP (AFAP)** is caused by mutations in the 3' and 5' sections of the APC gene and tends to present with fewer polyps (10-99, average of 30), more proximally located polyps and a later age at diagnosis of colon cancer, (average age at diagnosis 50-55 years). Extraintestinal manifestations are unusual.¹,²

- **Gardner syndrome** is associated with colonic polyposis typical of FAP, as well as osteomas and soft tissue tumors (epidermoid cysts, desmoid tumors, and fibromas).¹

- **Turcot syndrome** is associated with colonic polyposis typical of FAP and central nervous system (CNS) tumors, usually medulloblastoma.¹

It is important to note that approximately 6% of Ashkenazi Jewish individuals have a polymorphism in the APC gene, I1307K, that is associated with predisposition to colorectal cancer.³ Genetic testing is available for this polymorphism, but clinical utility for medical management has not been established.² Therefore, testing for the I1307K mutation is considered investigational and is not covered.
Familial Adenomatous Polyposis

APC-associated polyposis is inherited in an autosomal dominant manner; 70-80% of affected individuals have an affected parent. Therefore, 20-30% of APC mutations are de novo, meaning that this is a new mutation in the family; no family history of FAP is present. Individuals who are at risk for FAP should be offered colonoscopy yearly, usually starting at 10-12 years of age.\(^1,2\) Therefore, unlike most other adult-onset genetic conditions, it is appropriate to consider testing at-risk children for APC mutations at the age medical management decisions must be made.\(^4\) **Prenatal diagnosis for APC is not covered.**

Based on guidelines published by the National Comprehensive Cancer Network (NCCN) and the American Gastroenterological Society (AGA), APC gene testing may be considered when there is a known or suspected diagnosis of FAP or AFAP, or there is a known family history of an APC mutation.\(^2,4\)

**Criteria**

**Known APC Family Mutation(s) Testing**

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic APC mutation testing, AND
  - Diagnostic or Predisposition Testing:
    - Family History:
      - Known family mutation in APC identified in 1st degree relative(s), (Note: 2nd or 3rd degree relatives may be considered when 1st degree relatives are unavailable or unwilling to be tested), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**Full Sequence Analysis of APC**

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous APC mutation testing, and
  - No known familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals**:
  - **NCCN and AGA guidelines recommend APC genetic testing to confirm a diagnosis of FAP and to provide information about mutation location which may be helpful in predicting severity of polyposis, rectal involvement, and desmoid tumors. Additionally, this testing allows for mutation-specific testing in family members.\(^2,4\)**
    - Personal history
      - Known or suspected diagnosis of FAP (greater than 100 adenomatous polyps), or
      - Differential/suspected diagnosis of AFAP (10-100 adenomatous polyps), OR
    - Family history:
- First degree relative of an individual with a diagnosis of FAP or AFAP. (Note: Whenever possible, an affected family member should be tested first), OR
- Rendering laboratory is a qualified provider of service per the Health Plan policy

**Duplication/Deletion Analysis of APC†**

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous large rearrangement testing, and
  - Previous APC sequencing performed and no mutations found, and
  - No known familial mutation, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

†**Lab Test Restrictions:** Previous APC sequencing performed and no mutations found

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### Familial Adenomatous Polyposis

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### References

2. Colorectal Cancer Screening. **NCCN Clinical Practice Guidelines in Oncology.** V.I.2010. Available at: [www.nccn.org](http://www.nccn.org)
Fragile X Syndrome

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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specific sequence to be followed or additional information is required and must be supplied by the lab performing procedure(s) for full claim payment.

Description

Fragile X syndrome (FraX) is among the most common inherited forms of mental retardation. It is characterized by mental retardation, developmental delay, distinctive facial features in males (e.g., long facies, large ears), enlarged testicles (macro-orchidism), connective tissue problems, and speech/language disorders. In males, these features become more prominent with age, and therefore can be difficult to distinguish in infancy and early childhood. Females have more subtle features but may also be affected.

One gene – FMR1 – is associated with FraX. The condition is caused by a DNA expansion called a trinucleotide repeat. The number of CGG DNA repeats varies among individuals and can be classified into four groups depending on the number of repeats: unaffected, intermediate, premutation (carrier or possibly affected with fragile X associated tremor/ataxia (FXTAS)) and full mutation (affected status). The typical FMR1 gene has <45 repeats. An FMR1 gene with 45-54 repeats is considered an intermediate size; it is this range where the gene can expand or possibly contract. The premutation range is between 55-200 repeats and can also expand to a full mutation. Once an allele has a repeat size greater than 200 repeats, the gene has a full mutation and it is methylated (turned off).1-5

When the gene is passed onto another generation, a phenomenon called anticipation is seen. This means that the gene will expand as it is passed to each generation, and tends to expand more quickly when it is passed from mother to child than from father to child. The larger the size of the allele and the fewer the number of AGG repeats in the CGG tract the more likely it is for expansion to occur.3,4

Fragile X is inherited in a X-linked inheritance pattern; therefore the condition is typically seen in males, with females being less severely affected to unaffected carriers. This means that females have a 50% chance of passing the condition on to a son, who could be affected, and a 50% chance of passing it on to a daughter, who could be a carrier or be symptomatic. The size of an inherited repeat will determine whether a male child is affected. If a male inherits a premutation from his mother, all of his daughters will be carriers and none of his sons will be affected. It is estimated that one in 250 women are carriers for a FMR1 pre- or full-mutation, and one in 3600 males and one in 4000-6000 females are affected.1

Carriers of a premutation allele typically have more symptoms with age with about half of people affected with tremor or ataxia in their seventh decade. The risk and severity of FXTAS seems to be associated with the size of the repeat, with larger repeats having a greater risk and more severe symptoms.1 Women with a FMR1 premutation have a 20% chance of premature ovarian failure. Fragile X-associated ovarian failure
Fragile X is commonly called fragile X-associated primary ovarian insufficiency. The likelihood that a woman with sporadic ovarian failure is a carrier of Fragile X is approximately 3%. However, in women with a family history of premature ovarian failure, this risk is approximately 12%. Any woman with a personal or family history of premature ovarian failure, or high levels of follicle stimulating hormone before age 40, should consider testing for \textit{FMR1}. Preventive use of genetic testing on a population wide basis, for any condition, may be cost-effective if genotypic information can be shown to predict disease risk. Population-wide screening is ethically justifiable only if there is an efficacious and cost-effective intervention to prevent the disorder in those who are identified as being at increased risk. Although the DNA test is very accurate, it is important to ensure that effective means are in place to adequately counsel tested populations about the meaning and implications of the results. The nature of different phenotypes as a result of the gene expansion is complex. At this time, population wide carrier screening for Fragile X syndrome is not recommended.

Diagnosis of Fragile X is made by targeted mutation analysis, sequence analysis, FISH or deletion analysis of the \textit{FMR1} gene. Targeted mutation analysis, including the use of PCR and/or Southern Blot, can detect >99% of all cases. Sequence analysis, FISH and deletion analysis each detects <1% of cases. Other types of testing include methylation studies to determine if an allele with a premutation has fully or partially methylated gene leading to symptoms of Fragile X.

Once a deleterious mutation has been identified, relatives of affected individuals can be tested. Prenatal testing is available to individuals with a known family mutation. Genetic testing can be performed on amniocytes obtained through amniocentesis or chorionic villi obtained through chorionic villus sampling.

The National Society of Genetic Counselors (NSGC) advocates for genetic counseling for individuals and families who are undergoing genetic testing and at-risk family members. Genetic testing to determine carrier status or confirm a diagnosis is important for medical management of symptoms and potential issues that are associated with being a carrier such as FXTAS and premature ovarian failure. The NSGC does not support genetic testing for children where medical benefit is unknown. The American Society of Human Genetics/American College of Medical Genetics (ASHG/ACMG) also agrees that genetic testing in children for adult onset conditions should occur under specific circumstances where psychological, medical and reproductive benefits are apparent for the individual being tested. The ACMG also put out a statement for genetic testing for Fragile X. The statement indicates that genetic testing is available for individuals at risk for Fragile X syndrome. This includes individuals meeting the following clinical criteria: individuals with DD/MR/Autism and physical or behavioral characteristics of FraX, a family history of FraX, a positive chromosome analysis in the past but no confirmatory molecular testing, individuals with ovarian dysfunction, tremor/ataxia syndrome, and fetuses of known carrier mothers.

Genetic testing is considered medically necessary to confirm a diagnosis or carrier status in anyone who meets clinical criteria for Fragile X or FXTAS. Additionally, genetic testing should be approved to determine the carrier status in an at risk relative with a known family mutation. Individuals who meet clinical criteria for Fragile X syndrome testing should be offered mutation analysis. Finally, individuals with a family history of a known \textit{FMR} expansion should be offered testing. Full sequencing, FISH, and deletion/duplication analysis are not considered medically necessary at this time.
Criteria

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

- Genetic Counseling:
  - Medical evaluation by a physician familiar with Fragile X, and
  - Pre and post-test counseling by a medical geneticist or genetic counselor, AND
- Previous Genetic Testing:
  - No previous molecular genetic testing of FMR1, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Males and females with speech and/or language delay, motor development delay, mental retardation (MR), or autism, and the following have been ruled out:
    - Fragile XE syndrome, OR
  - Female with premature ovarian failure (cessation of menses before age of 40 years), OR
  - Males and females ≥50 years with progressive intention tremor and cerebellar ataxia of unknown origin, OR
- Prenatal Testing for At-Risk Pregnancies:
  - CGG trinucleotide repeat expansion in FMR1 identified in biologic mother*, OR
* Note: CVS must be interpreted with caution. The number of CGG repeats in the fetus can be accurately determined; however, often the methylation status of FMR1 is not yet established in chorionic villi at the time of sampling. CVS results may lead to a situation in which follow-up amniocentesis is necessary to resolve an ambiguous result.
- Carrier Screening and Predictive Testing for Presymptomatic/Asymptomatic At Risk Individuals:
  - Known CGG trinucleotide repeat expansion in FMR1 in 1st, 2nd, or 3rd degree biologic relative, or
  - Family history of premature ovarian failure (cessation of menses before age of 40 years), or
  - Family history of movement disorder and
    - Cerebellar ataxia has been ruled out
    - Other movement disorders have been ruled out, or
  - Family history of undiagnosed MR, or
  - Prior cytogenetic test suspicious for fragile X, OR

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Fragile X Syndrome

FL, PR, VI
### References

Gaucher Disease

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Description

Gaucher Disease (GD) is an autosomal recessive condition resulting from mutations in GBA, which creates deficiency of the enzyme glucocerebrosidase (also called beta-glucosidase). It is characterized by specific bone lesions, enlarged liver and spleen (hepatosplenomegaly) and changes within the blood cells, or signs of central nervous system (CNS) involvement. Some individuals exhibit a Parkinsonian type disease. Clinical signs alone are not diagnostic of GD.

There is a varying level of severity of GD, ranging from a perinatal lethal form to an asymptomatic form. Three of the forms are graded by type and the remaining two are descriptive. Type 1 is considered mild and characterized by the presence of clinical or radiographic evidence of bone disease (e.g. osteopenia, focal lytic or sclerotic lesions, and osteonecrosis), hepatosplenomegaly, blood disorders such as anemia and thrombocytopenia, lung disease, and the absence of primary central nervous system disease. Individuals with type 1 GD, however, may have CNS disease secondary to bone disease (e.g. spinal compression, osteopenia). Some individuals with GD type 1 exhibit a Parkinsonian type disease. Types 2 and 3 are generally distinguished by the age of onset, progression of the disease, primary CNS disease, and the presence of bone lesions. Type 2 has a typical onset prior to age 2 with a rapidly progressive course without the typical bone lesions. Type 3 is generally later onset, although it can have an onset earlier than 2 years of age, with a slower progression of symptoms, and the presence of bone lesions. Additionally, a perinatal-lethal form and a cardiovascular type have been described.

GD is seen in all populations. There is a founder effect, with certain alleles seen more frequently in specific populations, such as the Ashkenazi Jewish, Swedish and Jenin Arab, Greek and Albanian populations. Despite specific alleles being seen in these populations, type 1 GD is seen more frequently in the Ashkenazi Jewish population. It is estimated that 1 in 18 Ashkenazi Jewish individuals is a carrier for this condition. The prevalence of GD type 2 and 3 is unknown; however it appears to be more common in non-Caucasian populations. Genotype-phenotype correlation has been observed, but is imperfect as significant overlap of symptoms can occur. In general, one common allele in the Ashkenazi Jewish population, N370S, is associated with milder symptoms. Individuals with this allele in a heterozygous state generally do not develop neurological symptoms, and if found in the homozygous state tend to have the most mild phenotype, with many being asymptomatic and not coming to clinical attention.
GD is inherited in an autosomal recessive inheritance pattern. Because GD is recessive, individuals usually do not have other affected family members. However, some individuals affected with GD may not exhibit any symptoms, therefore an affected individual may have other family members who are affected as well, but are asymptomatic. Parents of an affected individual are obligate carriers, while siblings have a 50% chance of being carriers of the condition and a 25% chance of being affected. Carriers of GD are asymptomatic and do not exhibit any features of the condition.

A diagnosis of GD occurs through biochemical testing for acid β-glucosylceramidase enzyme activity, molecular genetic testing through targeted mutation analysis for the common founder mutations or sequence analysis of the GBA gene. Targeted mutation analysis will detect ~90% of cases in the Ashkenazi Jewish population, and ~50-60% of carriers in non-Jewish populations. Individuals who are not Jewish tend to be heterozygous for the N370S allele and either a rarer known allele or a unique allele. Sequence analysis may be able to detect an additional 2.6% of mutations in the Ashkenazi Jewish population, as well as mutations in other populations.6,9-11 Targeted mutation analysis for 11 alleles is available clinically, and can identify up to 98% of carriers.

Preventive use of genetic testing on a population wide basis, for any condition, may be cost-effective if genotypic information can be shown to predict disease risk. Population-wide screening is ethically justifiable only if there is an efficacious and cost-effective intervention to prevent the disorder in those who are identified as being at increased risk. Therefore, population wide carrier screening for GD is not recommended unless an individual is of Ashkenazi Jewish descent.6 However, because GD can be so mild that an affected individual may not come to clinical attention, there is debate on whether population wide screening is even efficacious and cost-effective in this population.

Targeted mutation analysis of GBA is available as a single multiplex assay for individuals of Ashkenazi Jewish descent. The Ashkenazi Jewish panel targets mutations associated with several autosomal recessive conditions with increased prevalence in this population. This can be practical from a convenience and cost perspective. However, an individual should be consented for each condition in the panel. If an individual does not consent to being tested for a particular condition, then each test should be ordered individually.6,12 Please see the Ashkenazi Jewish Screening Panel policy for more information.

The American College of Medical Genetics (ACMG) supports offering carrier testing for GD to individuals of Ashkenazi Jewish descent of testing for four common mutations. It is anticipated that the detection rate will be ~90%. This test should be offered to individuals of reproductive age, preferentially prior to pregnancy, with genetic counseling performed by a genetic counselor or medical geneticist. Counseling should include the following: 1) a description of the condition, 2) discussion of carrier risk associated with a negative test result, 3) the risk of passing the gene onto future offspring, and 4) discussion of the implications of a positive test on other family members. For GD, a discussion that carrier testing may identify someone who carries two disease causing alleles, but is asymptomatic. ACMG supports the testing of individuals of AJ descent, even when their partner is non-Ashkenazi Jewish. In this situation, testing would start with the individual who is Jewish and reflex back to the partner if necessary.6

The American College of Obstetrics and Gynecologists (ACOG) recommends individuals considering a pregnancy or are pregnant should consider testing if at least one member of the couple is Ashkenazi Jewish or has a relative with GD. If the woman is pregnant, testing may need to be conducted on both partners simultaneously (if one or both partners are Ashkenazi Jewish) in order to receive results in a timely fashion. If one or both partners are found to be carriers of GD, genetic counseling should be provided, and
prenatal testing offered, if appropriate. As a result of the above guidelines, CareCore has determined that genetic testing should be approved to confirm a diagnosis in anyone who meets clinical criteria for Gaucher Disease. Additionally, genetic testing should be approved to determine carrier status in an at risk relative with a known genetic mutation or the partner of a carrier or affected person with the understanding that asymptomatic individuals may be identified as having two disease alleles. Individuals who have a family member with a known GD mutation(s) should be tested for that/those mutation(s) first with the option of sequencing as per policy. Individuals of non-Ashkenazi Jewish descent who meet clinical criteria for GD should be offered sequence analysis. Finally, individuals of Ashkenazi Jewish descent should be offered carrier testing of the common mutations in this population. If they test negative and do not meet any other criteria for genetic testing, they should not continue on to sequence analysis.

Healthcare management after diagnosis includes treatment for current manifestations, as well as prevention for secondary complications. Bone marrow transplantation (BMT) and enzyme replacement therapy (ERT) have brought more permanent relief from symptoms. BMT can benefit those with severe GD. ERT, specifically, has changed the natural history of the disease, but requires treatment indefinitely. Some individuals may benefit from both BMT and ERT. However, those that do not undergo BMT or ERT may require symptomatic treatment through other means including medications, supplements, surgery and transfusions. Individuals with thrombocytopenia should avoid the use of non-steroidal anti-inflammatory drugs (NSAIDs).

Criteria

Carrier Testing

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

Known GBA Family Mutation(s) Testing

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous molecular genetic testing of GBA, AND
- Carrier Screening:
  - GBA mutation(s) identified in 1st, 2nd, or 3rd degree biologic relative(s), OR
- Prenatal Testing for At-Risk Pregnancies:
  - GBA mutation(s) identified in both biologic parents.

GBA Targeted Mutation Analysis for Ashkenazi Mutations (Four Mutations)

- Genetic Counseling: Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous GBA genetic testing, including Ashkenazi Jewish screening panels containing targeted mutation analysis for Gaucher disease, AND
  - Carrier Screening:
o Ashkenazi Jewish descent, regardless of disease status and results of glucosylceramidase assay,* and
o Intention to reproduce

*Ashkenazi Jewish individuals are recommended to have the full AJ Panel regardless of symptoms of disease. See Ashkenazi Jewish Disease Carrier Screening policy.

**Diagnostic and Expanded Carrier Testing**

**GBA Full Sequence Analysis†**

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous GBA full sequencing analysis, and
  - If Ashkenazi Jewish, testing for 4 common mutations is negative, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Glucosylceramidase enzyme activity in peripheral blood leukocytes is 0-15% of normal activity, and
  - Characteristic bone changes including osteopenia, focal lytic or sclerotic bone lesions or osteonecrosis, or
  - Hepatosplenomegaly and hematologic changes including anemia or thrombocytopenia, or
  - Primary neurologic disease which could include one or more of the following: cognitive impairment, bulbar signs, pyramidal signs, oculomotor apraxia, or seizures (progressive myoclonic epilepsy), OR
- Diagnostic Testing for Asymptomatic Carriers:
  - One mutation detected by targeted mutation analysis, and
  - Glucosylceramidase enzyme activity in peripheral blood leukocytes is 0-15% of normal activity, OR
- Testing for Individuals with Family History or Partners of Carriers:
  - 1st, 2nd, or 3rd degree biologic relative with Gaucher disease clinical diagnosis, family mutation unknown and testing unavailable, or
  - Partner is monoallelic or biallelic for GBA mutation, and has the potential and intention to reproduce with this partner.

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| FL, PR, VI |                |                         |                      |              |

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VA, NC, SC, WV


81251 GBA GENE  No  No  Yes

See LCD jurisdictions that refer to MolDX.

LCD: MolDX (http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Excluded%20Tests~94NNTX4657?open&navmenu=Browse*By*Topic|)

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GSTP1 Testing, Prostate Cancer

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Description

Prostate cancer is the most common non-skin cancer in men in the U.S., and the second leading cause of male cancer mortality.¹ Studies have shown that the GSTP1 gene is hypermethylated in the majority of prostate cancer patients.²⁻⁴ Several studies have examined the clinical validity of using GSTP1 analysis as an aid in the diagnosis of prostate cancer. While some studies have found a high correlation between GSTP1 methylation and prostate cancer², others have shown no significant association.⁴

Criteria

GSTP1 testing for prostate cancer is considered investigational at this time, and is not indicated for routine prostate cancer screening.

References

Hemochromatosis

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Description

- Hereditary hemochromatosis (HH) is an autosomal recessive genetic disorder that leads to excess iron absorption and storage in the liver, heart, pancreas, and other organs.¹
- Symptoms of hemochromatosis may include:¹ ²
  - Hepatomegaly, liver disease, jaundice, cirrhosis, liver cancer
  - Heart disease, arrhythmia, cardiomyopathy
  - Unexplained weakness, chronic fatigue, apathy
  - Arthritis, arthralgia
  - Increased skin pigmentation (bronze color)
  - Weight loss, hair loss
  - Hypothyroidism, hypopituitarism
  - Amenorrhea, early menopause
  - Loss of libido, impotence
  - Adult-onset diabetes
- HH is caused by mutations in the HFE gene.¹ About 1 in 200 to 1 in 400 people in the U.S. are affected with HH.¹
- HH is most common in Caucasians, with up to 11% of the population being carriers. The disorder is less common in African Americans and Hispanics, with the carrier prevalence being 2.3% and 3% respectively. HH is very rare in Asians, with less than 1 in 1000 being carriers.¹
- HH can be effectively treated in most people. Phlebotomy therapy can alleviate almost all symptoms of iron overload if initiated before organ damage occurs.³
- There are three common changes in the HFE gene associated with HH: C282Y, H63D, and S65C.¹
  - C282Y and H63D are the most common and account for 87% of hereditary hemochromatosis in European populations.¹
  - Many labs do not test for S65C because it accounts for <1% of hereditary hemochromatosis.¹
  - The combination of these mutations determines both the chances of symptoms occurring and their severity.
- The American Association for the Study of Liver Diseases (AASLD) Practice Guidelines (2001):⁴
  - "Genotyping to detect HFE mutations should be performed for all individuals who have abnormal iron studies and on those who are first-degree relatives of identified homozygotes."
Screening for Hereditary Hemochromatosis: A Clinical Practice Guideline from the American College of Physicians (2005):2
  o "Physicians should discuss the risks, benefits, and limitations of genetic testing in patients with a positive family history of hereditary hemochromatosis or those with elevated serum ferritin level or transferrin saturation. Before genetic testing, individuals should be made aware of the benefits and risks of genetic testing. This should include discussing available treatment and its efficacy; costs involved; and social issues, such as impact of disease labeling, insurability and psychological well-being, and the possibility of as-yet-unknown genotypes associated with hereditary hemochromatosis."

Criteria
Consideration for HFE genetic testing for hereditary hemochromatosis is determined according to diagnostic guidelines from the American Association for the study of Liver Disease and the American College of Physicians.2,4

Current guidelines support HFE genetic testing in people with:
  - Serologic evidence of iron overload, defined as transferrin saturation >45% and elevated ferritin
  - A known family history of hemochromatosis
  - A known familial mutation in the HFE gene in a first degree relative

Iron studies are the FIRST step in the diagnostic process and should be considered in individuals with some combination of the following signs and symptoms:
  - Hepatomegaly, cirrhosis, and hepatocellular carcinoma
  - Cardiomyopathy and arrhythmias
  - Diabetes mellitus type I and II
  - Impotence and loss of libido
  - Amenorrhea, Infertility
  - Arthritis and arthralgia (particularly in metacarpophalangeal joints)
  - Progressively increased skin pigmentation ("bronzing" of the skin)

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Hemochromatosis


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Hemoglobinopathies

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<td>Alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease gene analysis (HBA1/HBA2, alpha globin 1 and alpha globin 2), for common deletions or variants (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)</td>
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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

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Description

Hemoglobinopathies include genetic changes in the alpha- and beta-globin genes, which cause alpha-thalassemia, beta-thalassemia, sickle cell anemia, and other less common blood disorders. The American College of Obstetricians and Gynecologists (ACOG) states that carrier screening for hemoglobinopathies is appropriate for people with African, Mediterranean, and/or Southeast Asian ancestry who are pregnant or planning a pregnancy. However, they note that carrier frequencies may be higher in some other ethnic populations as well.

Criteria

Hemoglobinopathy screening by red blood cell indices (complete blood count) and quantitative hemoglobin analysis may be considered when ANY of the following are met:

- The individual is planning a pregnancy or currently pregnant AND at least one member of the couple is in an at-risk population. (This includes but may not be limited to people of African, Southeast Asian, and/or Mediterranean ancestry.); OR
- The individual has a family history of a hemoglobinopathy; OR
- The individual’s partner is a known carrier or affected with a hemoglobinopathy; OR
- The individual is participating in college athletics, military training, or other strenuous activity in which a carrier may become symptomatic.

Molecular genetic testing may be considered when ANY of the following are met:

- The individual is known or suspected to be a carrier of a hemoglobinopathy based on the results of red blood cell indices and hemoglobin analysis, ethnic background, and/or family history AND
Mutation confirmation is needed to verify carrier status, or for consideration of preimplantation or prenatal diagnosis; OR

- The individual has a family history of a hemoglobinopathy and the familial mutations are known.

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<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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See LCD jurisdictions that refer to MolDX.

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References

### Hereditary Cancer Syndrome Multi-Gene Panels

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Hereditary Cancer Syndrome

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Click here for applicable Medicare NCD/LCD information

Description

DNA sequencing techniques became available in the early 1970’s based on the work of Walter Gilbert and Frederick Sanger. Until recently, most sequencing-based testing used principles from this early work and was commonly called Sanger sequencing. Sanger technology sequences one stretch of DNA at a time. It relies on labeling the last nucleotide in each of many DNA fragments with something detectable, like radiation or fluorescent molecules, and then separating the DNA fragments by electrophoresis. Because each nucleotide (A, T, G, and C) is labeled differently, the nucleotides can be read in order based on different fragment sizes. This process is relatively labor intensive and did not lend itself to high-throughput applications. The limitations of Sanger sequencing have catalyzed the development of next generation sequencing (NGS) technologies.

NGS sequencing refers to several newer technologies that have been developed since about 2005 (sometimes referred to as massively parallel sequencing). These technologies generally involve breaking many copies of large stretches of DNA (or all genomic DNA) into smaller random-sized fragments, sequencing the smaller fragments (often in 35-500 base pair stretches), and then using informatics to match the overlapping DNA fragment sequencing results to create complete sequence data for the larger section of DNA. There are many approaches to NGS with common, currently used technologies including cyclic reversible termination, pyrosequencing, sequencing by ligation, and real-time sequencing.

The low cost and fast turnaround time of NGS have made sequencing large amounts of DNA feasible for clinical laboratory diagnostics. DNA sequencing by NGS can be applied to varying amounts of genetic information, such as large sets of genes, whole-exome (all parts of genes translated into protein), or whole-genome sequencing. The efficiency of sequencing many genes in parallel has led to an increasing number of large, multi-gene testing panels available on a clinical basis.

The benefits of NGS bring with it challenges as with any new technology. NGS sequencing platforms and the associated hardware needed to run them have large capital and maintenance costs for clinical laboratories and academic medical centers. Interpretation of large amounts of sequence information is a challenge for both laboratories and clinical geneticists. This is requiring new hardware and software for storage, analysis, and interpretation of NGS data. Bioinformatics may be largest impediment to the routine use of NGS in clinical practice.
NGS technology has a number of limitations. It does not perform as well as Sanger in certain applications. In addition, data are sometimes obtained that cannot be adequately interpreted based on the current knowledgebase. Furthermore, there are ethical challenges regarding the consent and patient disclosure of unanticipated, potentially harmful DNA variants. Finally, in some clinical cases, a more targeted approach involving fewer genes may be clinically superior to performing large panels involving sequencing of large amounts of DNA.

Guidelines and Evidence

The National Comprehensive Cancer Network (NCCN) states the following about next generation sequencing testing panels for hereditary cancer syndromes:

“These panels are intended for individuals who have tested negative for high penetrance genes (eg, BRCA1/2) and for those whose family history is suggestive of more than one syndrome...Limitations of these panels include an unknown percentage of variants of unknown significance, uncertainty of level of risk associated with most of these genes, and lack of clear guidelines on risk management of carriers of some of these mutations. Because of the complexity and limited data regarding their clinical utility, hereditary multi-gene cancer panels should only be ordered in consultations with a cancer genetics professional.”

The American College of Medical Genetics has a policy statement that offers general guidance on the clinical application of large-scale sequencing focusing primarily on whole exome and whole genome testing. However, some of the recommendations regarding counseling around unexpected results and variants of unknown significance and minimum requirements for reporting apply to many applications of NGS sequencing applications.

Criteria

When a patient meets medical necessity criteria for any hereditary cancer syndrome gene(s) included in a multi-gene panel, genetic testing for the clinically indicated gene(s) will be covered. See those gene-specific policies for guidance.

However, any genes that are included in a multi-gene panel but do NOT meet medical necessity criteria will NOT be a covered service. It will be at the laboratory, provider, and patient’s discretion to determine if a multi-gene panel remains the preferred testing option.

The following table summarizes some of the available hereditary cancer syndrome multi-gene panels and gene-specific coverage (see numbered footnotes for coverage guidance).
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<th>Gene</th>
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1. See the test-specific policy for this condition.
2. See the General Coverage Guidance section of the Hereditary Cancer Syndromes policy.
3. Not covered strictly for hereditary cancer indication. In general, genes that have only a low to moderate impact on cancer risk, as compared to high penetrance cancer syndrome-causing genes, and no clear management guidelines associated with identifying a mutation are not covered.

a. Tests provided by University of Washington Department of Laboratory Medicine and described as next generation sequencing of all exons and flanking intronic sequences, plus large deletion and duplication testing.

b. Tests provided by Ambry Genetics and described as next generation sequencing of all coding exons plus at least 5 bases into flanking introns and untranslated regions (except EPCAM), as well as gross deletions and duplications.

c. Tests provided by Mayo Medical Laboratories and described as including next-generation sequencing, Sanger sequencing, array comparative genomic hybridization, and multiplex ligation-dependent probe amplification to evaluate for the genes listed on the panel.

## Hereditary Cancer Syndrome Multi-Gene Panels

See LCD jurisdicutions that refer to MolDX.

LCD: MolDX

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse*By*Topic|||)

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<th>Code</th>
<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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<td>MOPATH PROCEDURE LEVEL 4</td>
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<td>N/A</td>
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<td>81404</td>
<td>MOPATH PROCEDURE LEVEL 5</td>
<td>No</td>
<td>No</td>
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</table>

VHL (von Hippel-Lindau tumor suppressor
PRSS1 (protease, serine, 1 [trypsin 1])
Hereditary Cancer Syndrome

VHL (von Hippel-Lindau tumor suppressor)  No  No  N/A

References

Hereditary Breast and Ovarian Cancer (BRCA1/2 Single Site Analysis)

<table>
<thead>
<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Procedure Code(s)</th>
<th>Requires:</th>
<th>Lab Procedure Restrictions†</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
<td>81215</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
<td>81217</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

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† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Click here for applicable Medicare NCD/LCD information

What Is Hereditary Breast and Ovarian Cancer?

- Hereditary breast and ovarian cancer (HBOC) is an inherited form of cancer characterized by:\(^1\):
  - Personal history of breast cancer at a young age (typically under age 50)
  - Personal history of two primary breast cancers
  - Personal history of both breast and ovarian cancer
  - Personal history of a triple negative breast cancer (ER-, PR-, HER2-)
  - Personal history of ovarian/fallopian tube/primary peritoneal cancer
  - Multiple cases of breast and/or ovarian cancer in a family
  - Personal or family history of male breast cancer
  - Personal or family history of pancreatic cancer with breast or ovarian cancer
  - Previously identified BRCA1/2 mutation in the family
  - Any of the above with Ashkenazi Jewish ancestry

- Up to 10% of all breast cancer is associated with an inherited gene mutation, with BRCA1/2 accounting for about 20-25% of all hereditary cases.\(^1\)\(^4\)

- About 1 in 400 people in the general population has a BRCA1/2 mutation. The prevalence of mutations is higher in people of Norwegian, Dutch or Icelandic ethnicity.\(^1\) The prevalence of BRCA mutations varies among African Americans, Hispanics, Asian Americans, and non-Hispanic whites.\(^2\)

- About 1/40 people of Ashkenazi Jewish ancestry has a BRCA1/2 mutation. The majority of the risk in the Ashkenazi Jewish population is associated with three common founder mutations, two of which are in the BRCA1 gene and one in the BRCA2 gene. These three mutations account for 98-99% of identified mutations in the Ashkenazi Jewish population.\(^1\)\(^6\)

- People with a BRCA mutation have an increased risk of breast cancer (40-80%), ovarian cancer (11-40%), male breast cancer (1-10%), prostate cancer (up to 39%), pancreatic cancer (1-7%), and several other types of cancer.\(^1\) Screening and prevention options are available to specifically address the increased risk of these cancers in a person with a BRCA mutation.\(^1\)
• BRCA mutations are inherited in an autosomal dominant manner. Children of an affected individual have a 50% risk to inherit the susceptibility gene. The risk for breast and ovarian cancer varies among family members and between families.
• Other inherited cancer syndromes that can include breast cancer are Li-Fraumeni syndrome, Cowden syndrome, Hereditary Diffuse Gastric Cancer syndrome, and Peutz Jeghers syndrome.

Test Information
• Four types of BRCA testing are available. Each may be appropriate for different clinical situations.
• Single site testing looks for a specific mutation in either the BRCA1/2 gene previously identified in a family member.
  o This test is appropriate for those who have a known BRCA mutation in the family AND are not Ashkenazi Jewish.
  o It is important to note that founder mutation testing may be appropriate for those with Ashkenazi Jewish ancestry, even with a known familial mutation, since these mutations are common enough that multiple mutations can be found in the same Ashkenazi Jewish individual or family. If the familial mutation is not one of the three Ashkenazi Jewish mutations, then single site testing for that mutation should be performed in addition to the founder mutation panel.
• Other testing options (see related summaries for details):
  o Ashkenazi Jewish founder mutations
  o Full sequence testing
  o Large rearrangement testing

Guidelines and Evidence
The National Comprehensive Cancer Network (2014) evidence and consensus-based guidelines include recommendations for those with a known mutation in the family. These recommendations are category 2A, defined as "lower-level evidence with uniform NCCN consensus."
• Based on these guidelines, and the recommendations of the National Society of Genetic Counselors (2013), single site analysis is appropriate for non-Ashkenazi Jewish individuals from a family with a known BRCA1/2 mutation.

Criteria
• Genetic Counseling
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing:
  o No previous full sequence testing or large rearrangement testing, AND
• Known family mutation in BRCA1/2 identified in 1st, 2nd, or 3rd degree relative(s), AND
  o Age - 18 years or older, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.
<table>
<thead>
<tr>
<th>NCD/LCD Jurisdiction and CPT Codes</th>
<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Hereditary Breast Ovarian Cancer Syndrome</strong></td>
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<tr>
<td>AZ, MT, ND, UT, WY, SD, ID, AK, WA, OR</td>
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<td>81215 BRCA1 GENE KNOWN FAM VARIANT</td>
<td>Yes</td>
<td>Yes (Group 1)</td>
<td>No</td>
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<tr>
<td></td>
<td>81217 BRCA2 GENE KNOWN FAM VARIANT</td>
<td>Yes</td>
<td>Yes (Group 1)</td>
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<td>CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV</td>
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<td>81215 BRCA1 GENE KNOWN FAM VARIANT</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td></td>
<td>81217 BRCA2 GENE KNOWN FAM VARIANT</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>FL, PR, VI</td>
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<td>LCD: L33703 (<a href="http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33703&amp;ContrId=368&amp;ver=11&amp;Date=&amp;DocID=L33703&amp;SearchType=Advanced&amp;bc=KAAAAAgAAAAAAA%3d%3d&amp;">link</a>)</td>
<td>81215 BRCA1 GENE KNOWN FAM VARIANT</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>81217 BRCA2 GENE KNOWN FAM VARIANT</td>
<td>No</td>
<td>No</td>
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<td>81215 BRCA1 GENE KNOWN FAM VARIANT</td>
<td>No</td>
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<tr>
<td></td>
<td>81217 BRCA2 GENE KNOWN FAM VARIANT</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<td>See LCD jurisdictions that refer to MolDX.</td>
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<td>81215 BRCA1 GENE KNOWN FAM VARIANT</td>
<td>No</td>
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<tr>
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<td>No</td>
<td>No</td>
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**References**


Hereditary Breast and Ovarian Cancer (BRCA1/2 Ashkenazi Jewish Founder Mutations)

### Procedure(s) covered by this policy:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Code(s)</th>
<th>Requires:</th>
<th>Lab Procedure Restrictions†</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants</td>
<td>81212</td>
<td>Yes</td>
<td>No</td>
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</tbody>
</table>

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**What Is Hereditary Breast and Ovarian Cancer?**

- Hereditary breast and ovarian cancer (HBOC) is an inherited form of cancer characterized by:
  - Personal history of breast cancer at a young age (typically under age 50)
  - Personal history of two primary breast cancers
  - Personal history of both breast and ovarian cancer
  - Personal history of a triple negative breast cancer (ER-, PR-, HER2-)
  - Personal history of ovarian/fallopian tube/primary peritoneal cancer
  - Multiple cases of breast and/or ovarian cancer in a family
  - Personal or family history of male breast cancer
  - Personal or family history of pancreatic cancer with breast or ovarian cancer
  - Previously identified BRCA1/2 mutation in the family
  - Any of the above with Ashkenazi Jewish ancestry

- Up to 10% of all breast cancer is associated with an inherited gene mutation, with BRCA1/2 accounting for about 20-25% of all hereditary cases.

- About 1 in 400 people in the general population has a BRCA1/2 mutation. The prevalence of mutations is higher in people of Norwegian, Dutch or Icelandic ethnicity. The prevalence of BRCA mutations varies among African Americans, Hispanics, Asian Americans, and non-Hispanic whites.

- About 1/40 people of Ashkenazi Jewish ancestry has a BRCA1/2 mutation. The majority of the risk in the Ashkenazi Jewish population is associated with three common founder mutations, two of which are in the BRCA1 gene and one in the BRCA2 gene. These three mutations account for 98-99% of identified mutations in the Ashkenazi Jewish population.

- People with a BRCA mutation have an increased risk of breast cancer (40-80%), ovarian cancer (11-40%), male breast cancer(1-10%), prostate cancer(up to 39%), pancreatic cancer(1-7%), and several other types of cancer. Screening and prevention options are available to specifically address the increased risk of these cancers in a person with a BRCA mutation.

- **BRCA** mutations are inherited in an autosomal dominant manner. Children of an affected individual have a 50% risk to inherit the susceptibility gene. The risk for breast and ovarian cancer varies among family members and between families.
• Other inherited cancer syndromes that can include breast cancer are Li-Fraumeni syndrome, Cowden syndrome, Hereditary Diffuse Gastric Cancer syndrome, and Peutz Jeghers syndrome.¹

Test Information

• Four types of BRCA testing are available. Each may be appropriate for different clinical situations.
  • Ashkenazi Jewish founder mutation testing includes the three mutations most commonly found in the Ashkenazi Jewish population: 187delAG and 5385insC in BRCA1 and 6174delT in BRCA2.¹
    o Testing for these three most common mutations detects about 98% of mutations in those with Ashkenazi Jewish ancestry.¹,⁶
    o This test is appropriate for those who meet criteria (see Guidelines below) AND have Ashkenazi Jewish ancestry.⁵-⁷
  • Other testing options (see related summaries for details):
    o Full sequence testing
    o Large rearrangement testing
    o Single site testing (known familial mutation)

Guidelines and Evidence

• The National Comprehensive Cancer Network (NCCN, 2014)⁶ evidence and consensus-based guidelines include unaffected women with a family history of cancer, those with a known mutation in the family, those with a personal history of breast cancer and/or ovarian cancer, those with a personal history of pancreatic and/or prostate (Gleason score at least 7) cancer, and men.
  o Based on these guidelines, and the recommendations of the National Society of Genetic Counselors (2013)⁷ the founder mutation analysis is appropriate for any individual with Ashkenazi Jewish ancestry with a personal history of breast, epithelial ovarian, fallopian tube, or primary peritoneal cancer. When there is a personal history of pancreatic or prostate (Gleason score at least 7) cancer, additional family history of hereditary breast ovarian cancer syndrome related cancers is required.
  o These recommendations are Category 2A, defined as "lower-level evidence with uniform NCCN consensus."
• The U.S. Preventive Services Task Force (USPSTF, 2013) recommendations address women who do not have a personal history of breast and/or ovarian cancer, but rather have a family history of these cancer types.⁸
• The USPSTF guideline recommends that primary care providers identify women who have a family history of breast, ovarian, fallopian tube, or peritoneal cancer with one of several screening tools. These tools are designed to identify woman who may be at an increased risk to carry a BRCA mutation. Women identified as high risk should then be referred for genetic counseling and, if indicated after counseling, BRCA testing.
  • Women identified as high risk by these screening tools typically have one of more of the following characteristics:
    o A first or second degree relative with breast cancer before 50y.o
    o A first or second degree relative with ovarian cancer
    o A first or second degree relative with bilateral/multifocal breast cancer
    o A first or second degree male relative with breast cancer
    o A first or second degree relative with both breast and ovarian cancers
- Two or more relatives (first, second, third degree) with breast and/or ovarian cancer
- Two or more relatives (first, second, third degree) with breast and/or prostate/pancreatic cancer
- Presence of Ashkenazi Jewish ancestry with any of the above
- The USPSTF considers this a level B recommendation: "The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms."

Criteria

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy) AND

- Previous Genetic Testing:
  - No previous full sequence testing, and
  - No previous large rearrangement testing, and
  - No previous Ashkenazi Jewish founder mutation testing, AND

- Age 18 years or older, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Ashkenazi Jewish descent, and
    - Epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnosis at any age, and/or
    - Male or female breast cancer diagnosis at any age, OR
    - Personal history of pancreatic cancer or prostate cancer (Gleason score at least 7) at any age with at least one close blood relative* with breast and/or ovarian and/or pancreatic and/or prostate cancer (Gleason score at least 7) at any age

- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Ashkenazi Jewish descent and a first or second degree relative meeting the following:
    - Epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnosis at any age, and/or
    - Male or female breast cancer diagnosis at any age, or
    - Personal history of pancreatic cancer or prostate cancer (Gleason score at least 7) at any age with at least one close blood relative* with breast and/or ovarian and/or pancreatic and/or prostate cancer (Gleason score at least 7) at any age, and
    - The affected relative is deceased, unable, or unwilling to be tested†, or
    - Close blood relative (1st, 2nd, or 3rd degree) with a known founder mutation in a BRCA1/2 gene, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

*First-degree relatives (parents, siblings, children); second-degree relatives (aunts, uncles, grandparents, grandchildren, nieces, nephews and half-siblings); and third-degree relatives (great-grandparents, great-aunts, great-uncles, and first cousins) on the same side of the family.
** Note: Full gene sequencing of BRCA1/2 is authorized if no founder mutations are detected by 81212 and the individual meets the criteria above. 6, 7
†Testing of unaffected individuals should only be considered when an affected family member is unavailable for testing due to the significant limitations in interpreting a negative result.
### NCD/LCD Jurisdiction and CPT Codes

<table>
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<th>Specific Tests</th>
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</table>

#### Hereditary Breast Ovarian Cancer Syndrome

**AZ, MT, ND, UT, WY, SD, ID, AK, WA, OR**


| 81212 BRCA1&2 185&385&6174 VAR | Yes | Yes (Group 1) | No |

**CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV**


| 81212 BRCA1&2 185&385&6174 VAR | No | No | Yes |

**FL, PR, VI**


| 81212 BRCA1&2 185&385&6174 VAR | No | No | No |

**VA, NC, SC, WV**


| 81212 BRCA1&2 185&385&6174 VAR | No | No | Yes |

See LCD jurisdictions that refer to MolDX.


| 81212 BRCA1&2 185&385&6174 VAR | No | No | N/A |

#### References


## Hereditary Breast and Ovarian Cancer (BRCA1/2 Full Sequence Analysis)

<table>
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<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Procedure Code(s)</th>
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<tr>
<td>BRCA1/2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1/2 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)</td>
<td>81211</td>
<td>Yes Yes</td>
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<tr>
<td>BRCA1/2 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)</td>
<td>81214</td>
<td>Yes Yes</td>
</tr>
<tr>
<td>BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
<td>81216</td>
<td>Yes Yes</td>
</tr>
</tbody>
</table>

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**Click here for applicable Medicare NCD/LCD information**

### What Is Hereditary Breast and Ovarian Cancer?

- Hereditary breast and ovarian cancer (HBOC) is an inherited form of cancer characterized by:
  - Personal history of breast cancer at a young age (typically under age 50)
  - Personal history of two primary breast cancers
  - Personal history of both breast and ovarian cancer
  - Personal history of a triple negative breast cancer (ER-, PR-, HER2-)
  - Personal history of ovarian/fallopian tube/primary peritoneal cancer
  - Multiple cases of breast and/or ovarian cancer in a family
  - Personal or family history of male breast cancer
  - Personal or family history of pancreatic cancer with breast or ovarian cancer
  - Previously identified BRCA1/2 mutation in the family
  - Any of the above with Ashkenazi Jewish ancestry

- Up to 10% of all breast cancer is associated with an inherited gene mutation, with BRCA1/2 accounting for about 20-25% of all hereditary cases.  
- About 1 in 400 people in the general population has a BRCA1/2 mutation. The prevalence of mutations is higher in people of Norwegian, Dutch or Icelandic ethnicity.  
- The prevalence of BRCA mutations varies among African Americans, Hispanics, Asian Americans, and non-Hispanic whites.
• About 1/40 people of Ashkenazi Jewish ancestry has a \textit{BRCA1/2} mutation. The majority of the risk in the Ashkenazi Jewish population is associated with three common founder mutations, two of which are in the \textit{BRCA1} gene and one in the \textit{BRCA2} gene. These three mutations account for 98-99\% of identified mutations in the Ashkenazi Jewish population.\textsuperscript{1,6}

• People with a \textit{BRCA} mutation have an increased risk of breast cancer (40-80\%), ovarian cancer (11-40\%), male breast cancer(1-10\%), prostate cancer(up to 39\%), pancreatic cancer(1-7\%), and several other types of cancer.\textsuperscript{1} Screening and prevention options are available to specifically address the increased risk of these cancers in a person with a \textit{BRCA} mutation.\textsuperscript{1}

• \textit{BRCA} mutations are inherited in an autosomal dominant manner. Children of an affected individual have a 50\% risk to inherit the susceptibility gene.\textsuperscript{1} The risk for breast and ovarian cancer varies among family members and between families.

• Other inherited cancer syndromes that can include breast cancer are Li-Fraumeni syndrome, Cowden syndrome, Hereditary Diffuse Gastric Cancer syndrome, and Peutz Jeghers syndrome.\textsuperscript{1}

\textbf{Test Information}

• Four types of \textit{BRCA} testing are available. Each may be appropriate for different clinical situations.

• \textbf{Full sequence analysis of \textit{BRCA1/2} genes} looks at all of the coding regions of the \textit{BRCA1/2} genes, and often includes analysis of five common \textit{BRCA1/2} gene duplications and deletions.
  - When full sequence analysis is negative, reflex testing for additional large rearrangements may be covered. Attestation of a negative full sequence result is required.
  - Full sequence testing is typically appropriate as an initial test for people who meet criteria (see Guidelines below) and do NOT have Ashkenazi Jewish ancestry.\textsuperscript{6, 7}

• Other testing options (see related summaries for details):
  - Ashkenazi Jewish founder mutation testing
  - Single site testing (known familial mutation)
  - Large rearrangement testing
  - Cancer Multigene Panels- \textit{BRCA1/2} gene testing is also available in the form of multigene panels for individuals with a personal and/or family history of cancer suggestive of more than one hereditary cancer syndrome.

\textbf{Guidelines and Evidence}

• The \textbf{National Comprehensive Cancer Network (NCCN, 2014)}\textsuperscript{6} evidence and consensus-based guidelines address test indications for those with a personal history of HBOC-related cancers, those with a known mutation in the family, and unaffected individuals with a family history of HBOC-related cancer.
  - Based on these guidelines, and the recommendations of the \textbf{National Society of Genetic Counselors (2013)}\textsuperscript{7}, \textit{BRCA} sequence analysis is appropriate in individuals with a personal and/or family history of cancer when any of the following criteria are met:
    • Personal history of breast cancer plus one or more of the following in non-Ashkenazi Jewish individuals:
      • Diagnosed at age 45 years or younger; OR
      • Diagnosed at age 50 or younger with at least one close blood relative with breast cancer diagnosed at any age, OR
- Diagnosed at age 60 years or younger with a triple negative (ER-, PR-, HER2-) breast cancer; OR
- Two breast primaries when the first breast cancer diagnosis occurred at age 50 or younger; OR
- Diagnosed at any age with at least one close blood relative* with breast cancer diagnosed at age 50 years or younger and/or at least one close blood relative* diagnosed with epithelial ovarian, fallopian tube or primary peritoneal cancer at any age; OR
- Diagnosed at any age with two or more close blood relatives* with breast cancer at any age; OR
- Diagnosed at any age with two or more close blood relatives* with pancreatic cancer or prostate cancer (Gleason score at least 7) at any age; OR
- Diagnosed at age 50 years or younger with an unknown or limited** family history; OR
- Close male relative* with breast cancer
  - Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer (without history of breast cancer).
  - Personal history of male breast cancer
  - Personal history of pancreatic cancer or prostate cancer (Gleason score at least 7) at any age with at least two close blood relatives* with breast and/or ovarian and/or pancreatic or prostate cancer (Gleason score at least 7) at any age
  - Family history only, no personal diagnosis of cancer plus either one of the following:
    - First- or second-degree blood relative meeting any of the above criteria OR
    - Third-degree blood relative with breast and/or ovarian cancer AND 2 or more close blood relatives* with breast cancer (at least one diagnosed at or before age 50) and/or ovarian, primary peritoneal, or fallopian tube cancer.
- NCCN states "Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing." They caution that the significant limitations in interpreting results from unaffected relatives must be discussed.
- Ashkenazi Jewish women who are negative for founder mutation testing, and have a high pre-test probability of carrying a BRCA mutation.(1,6)
  - Close blood relatives include: first-degree relatives (parents, siblings, children); second-degree relatives (aunts, uncles, grandparents, grandchildren, nieces, nephews and half-siblings); and third-degree relatives (great-grandparents, great-aunts, great-uncles, and first cousins) on the **same side of the family**.
  - **Limited family history is defined as "fewer than two first- or second-degree female relatives having lived beyond age 45 in either lineage."**
  - These recommendations are Category 2A, defined as "lower-level evidence with uniform NCCN consensus."
The U.S. Preventive Services Task Force (USPSTF, 2013) recommendations address women who do not have a personal history of breast and/or ovarian cancer, but rather have a family history of these cancer types. The USPSTF guideline recommends:

- "That primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (BRCA1/2). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing."
- The USPSTF considers this a level B recommendation: "The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms."
- The USPSTF guidelines no longer make explicit recommendations as to who should have BRCA1/2 gene testing -- only genetic counseling. In general, women identified as high risk by these screening tools have one or more of the following characteristics:
  - A first or second degree relative with breast cancer before 50y
  - A first or second degree relative with ovarian cancer
  - A first or second degree relative with bilateral/multifocal breast cancer
  - A first or second degree male relative with breast cancer
  - A first or second degree relative with both breast and ovarian cancers
  - Two or more relatives (first, second, third degree) with breast and/or ovarian cancer
  - Two or more relatives (first, second, third degree) with breast and/or prostate/pancreatic cancer
  - Presence of Ashkenazi Jewish ancestry with any of the above

Criteria

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy) 6, 8, 9, AND
- Previous Genetic Testing:
  - No previous full sequencing of BRCA1/2, and
  - No known mutation identified by previous BRCA analysis, AND
- Age - 18 years or older, AND
- Diagnostic Testing for Symptomatic Individuals: 6
  - Personal History:
    - Female with breast cancer diagnosis ≤45 years of age, and/or
    - Two breast primary tumors with first diagnosis ≤50 years of age and second diagnosis at any age (ipsilateral or bilateral), and/or
    - Diagnosed ≤60 years of age with estrogen receptor negative, progesterone receptor negative, and HER2 negative (triple negative) breast cancer and/or
    - Diagnosed ≤50 years of age with at least one close blood relative with breast cancer diagnosed at any age
    - Diagnosed ≤50 years of age with a limited family history (NCCN provides this guidance regarding limited family history: "individuals with limited family history, such as fewer than two first- or second- degree female relatives having lived
beyond 45 in either lineage, may have an underestimated probability of a familial mutation*), and/or
- Male with breast cancer at any age, and/or
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnosis at any age, OR
  - Personal & Family History Combination: 6
    - Initial breast cancer diagnosis at any age and one or more of the following:
      - Breast cancer in at least 1 close blood relative (first-, second-, or third-degree) ≤50 years of age, and/or
      - Epithelial ovarian, fallopian tube, or primary peritoneal cancer in at least 1 close blood relative (first-, second-, or third-degree) at any age, and/or
      - At least 2 close blood relatives (first-, second-, or third-degree on same side of family) with breast cancer at any age, or
      - At least 2 close blood relatives (first-, second-, or third-degree on same side of family) with pancreatic cancer or prostate cancer (Gleason score at least 7) at any age, and/or
      - Male close blood relative (first-, second-, or third-degree) with breast cancer, and/or
    - Personal history of pancreatic cancer or prostate cancer (Gleason score at least 7) at any age with ≥2 close blood relatives (on the same side of the family) with breast and/or ovarian and/or pancreatic and/or prostate cancer (Gleason score at least 7) at any age, OR
  - Predisposition Testing for Presymptomatic/Asymptomatic Individuals
    - Non-Ashkenazi Jewish descent, and one or more of the following: 1, 6
      - A first or second degree relative with breast cancer at age 45 or younger, or
      - A first or second degree relative with two primary breast cancers, with the first diagnosis occurring at age 50 or younger, or
      - A first or second degree relative with a triple negative breast cancer (ER-, PR-, her2-) occurring at age 60 or younger, or
      - A first or second degree relative with ovarian/fallopian tube/primary peritoneal cancer at any age, or
      - A first or second degree relative with male breast cancer at any age, or
      - A combination of two or more first or second degree relatives on the same side of the family with breast cancer, one of whom was diagnosed at age 50 or younger, or
      - A combination of three or more first or second degree relatives on the same side of the family with breast cancer regardless of age at diagnosis, or
      - A combination of both breast and ovarian/fallopian tube/primary peritoneal cancer among two or more first or second degree relatives on the same side of the family, or
      - A first or second degree relative with both breast and ovarian/fallopian tube/primary peritoneal cancer at any age, or
      - A first, second, or third degree relative with a known BRCA1/2 mutation, or
      - A combination of three or more first or second degree relatives on the same side of the family with breast or ovarian/fallopian tube/primary peritoneal cancer AND pancreatic or prostate (Gleason score ≥7) cancer at any age, or
- The probability of a BRCA mutation in the patient is greater than or equal to 10% as calculated by BRCAPRO, or
- Ashkenazi Jewish woman who is negative for founder mutation testing, and has a high pre-test probability of carrying a BRCA mutation† 1, 6 AND
  - Unaffected member is the most informative person to test. All affected family members are deceased, or all affected family members have been contacted and are unwilling to be tested, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

†First-degree relatives (parents, siblings, children); second-degree relatives (aunts, uncles, grandparents, grandchildren, nieces, nephews and half-siblings); and third-degree relatives (great-grandparents, great-aunts, great-uncles, and first cousins) on the same side of the family.

<table>
<thead>
<tr>
<th>NCD/LCD Jurisdiction and CPT Codes</th>
<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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<tr>
<td>Hereditary Breast Ovarian Cancer Syndrome</td>
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<td>Yes (Group 1)</td>
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VA, NC, SC, WV


81211 BRCA1&2 SEQ & COM DUP/DEL No No Yes
81214 BRCA1 FULL SEQ & COM DUP/DEL No No Yes
81216 BRCA2 GENE FULL SEQUENCE No No Yes

See LCD jurisdictions that refer to MolDX.

LCD: MolDX (http://www.palmettoga.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse^By^Topic|||)

81211 BRCA1&2 SEQ & COM DUP/DEL No No N/A
81214 BRCA1 FULL SEQ & COM DUP/DEL No No N/A

References

Hereditary Breast and Ovarian Cancer (BRCA1/2 Large Rearrangement Analysis)

**Procedure(s) covered by this policy:**

<table>
<thead>
<tr>
<th>Procedure Code(s)</th>
<th>Requires:</th>
<th>Lab Procedure Restrictions†</th>
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<tbody>
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<td>Yes</td>
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</tbody>
</table>

* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

**Click here for applicable Medicare NCD/LCD information**

**What Is Hereditary Breast and Ovarian Cancer?**

- Hereditary breast and ovarian cancer (HBOC) is an inherited form of cancer characterized by:
  - Personal history of breast cancer at a young age (typically under age 50)
  - Personal history of two primary breast cancers
  - Personal history of both breast and ovarian cancer
  - Personal history of a triple negative breast cancer (ER-, PR-, HER2-)
  - Personal history of ovarian/fallopian tube/primary peritoneal cancer
  - Multiple cases of breast and/or ovarian cancer in a family
  - Personal or family history of male breast cancer
  - Personal or family history of pancreatic cancer with breast or ovarian cancer
  - Previously identified BRCA1/2 mutation in the family
  - Any of the above with Ashkenazi Jewish ancestry

- Up to 10% of all breast cancer is associated with an inherited gene mutation, with BRCA1/2 accounting for about 20-25% of all hereditary cases.¹-⁴

- About 1 in 400 people in the general population has a BRCA1/2 mutation. The prevalence of mutations is higher in people of Norwegian, Dutch or Icelandic ethnicity.¹ The prevalence of BRCA mutations varies among African Americans, Hispanics, Asian Americans, and non-Hispanic whites.²

- About 1/40 people of Ashkenazi Jewish ancestry has a BRCA1/2 mutation. The majority of the risk in the Ashkenazi Jewish population is associated with three common founder mutations, two of which are in the BRCA1 gene and one in the BRCA2 gene. These three mutations account for 98-99% of identified mutations in the Ashkenazi Jewish population.¹,⁵,⁶

- People with a BRCA mutation have an increased risk of breast cancer (40-80%), ovarian cancer (11-40%), male breast cancer(1-10%), prostate cancer(up to 39%), pancreatic cancer(1-7%), and several other types of cancer.¹ Screening and prevention options are available to specifically address the increased risk of these cancers in a person with a BRCA mutation.¹

- BRCA mutations are inherited in an autosomal dominant manner. Children of an affected individual have a 50% risk to inherit the susceptibility gene.¹ The risk for breast and ovarian cancer varies among family members and between families.
Other inherited cancer syndromes that can include breast cancer are Li-Fraumeni syndrome, Cowden syndrome, Hereditary Diffuse Gastric Cancer syndrome, and Peutz Jeghers syndrome.¹

Test Information

Four types of BRCA testing are available. Each may be appropriate for different clinical situations.

- **Large rearrangement testing** looks for large rearrangements, duplications, and deletions in the BRCA1/2 genes. When a full sequence analysis is negative, reflex testing for these additional large rearrangements may be covered. Attestation of a negative full sequence result is required.

- Other testing options (see related summaries for details):
  - Ashkenazi Jewish founder mutation testing
  - Single site testing (known familial mutation)
  - Full sequence testing

Guidelines and Evidence

- The **National Comprehensive Cancer Network (2014)**⁶ guidelines state that: "Comprehensive genetic testing includes full sequencing of BRCA1/2 and detection of large genomic rearrangements."
- The **National Society of Genetic Counselors (2013)**⁷ guidelines also state that: "[For patients with negative sequencing results], it may be appropriate to request additional analysis to detect large genomic rearrangements in both BRCA1 and BRCA2 genes."
- In non-Ashkenazi Jewish individuals: If no mutation or inconclusive results are reported after sequence analysis, testing for large deletions/duplications in BRCA1/2 should be considered. ¹,⁶,⁷
- Frequency of gene rearrangements is reviewed in a 2010 study by Stadler et al:⁷
  - "Genomic rearrangements in the BRCA1 gene are found in 1.3-5.1% of families with histories highly suggestive of an inherited predisposition, accounting for 8-19% of all BRCA1 mutations."
  - "The prevalence of genomic rearrangements in the BRCA2 gene appears to be lower, with such alterations accounting for 0-11% of all BRCA2 mutations."
  - In their series of 108 patients with a qualifying history and negative results from BRCA1/2 sequencing, none had mutations found by rearrangement testing. The authors conclude: "Major gene rearrangements involving the BRCA1/2 genes appear to contribute little to the burden of inherited predisposition to breast and ovarian cancer in the Ashkenazim."
- Jackson et al 2014⁸ addresses the characteristics of individuals who are more likely to have a large rearrangements in BRCA1/2:
  - Latin American/Caribbean ancestry
  - Number of first-degree relatives with breast cancer (1 or more)
  - Younger age at first breast cancer diagnosis (average age of 39.8 years)
  - More likely to have ER- and PR- breast cancers
  - More likely to have more two breast cancers as well as ovarian cancer
  - More likely to have infiltrating ductal carcinoma with ductal carcinoma in situ features
## Criteria

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy) \(^6,9,10\), AND

- Previous Genetic Testing:
  - No previous BRCA large rearrangement testing, and
  - Meets criteria for full sequence analysis of BRCA1/2, and
  - Previous BRCA1/2 sequencing, and no mutations found†, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

### NCD/LCD Jurisdiction and CPT Codes

<table>
<thead>
<tr>
<th>Specific Tests</th>
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<tr>
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See LCD jurisdictions that refer to MolDX.

LCD: MolDX ([http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BM_LRK6738?open&navmenu=Browse*By*Topic|]])

| 81213 BRCA1&2 UNCOM DUP/DEL VAR |
| No | No | N/A |
References


## HLA-B*1502

<table>
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<th>Procedure Code(s)</th>
<th>Requires:</th>
<th>Lab Procedure Restrictions†</th>
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<tr>
<td>HLA-B*1502 testing for carbamazepine toxicity</td>
<td>81381</td>
<td>No</td>
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</tbody>
</table>

* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

### Description

Carbamazepine (Tegretol®, Tegretol XR®, Equetro®, Carbatrol®) is an antiepileptic agent used in the treatment of seizure disorders, psychiatric disorders, and pain from trigeminal neuralgia. Adverse drug reactions have been associated with carbamazepine use, including the significant dermatological conditions called Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN). A genetic variant of HLA-B, called HLA-B*1502, has been highly associated with carbamazepine-induced SJS and TEN in certain Asian populations. Product labeling for carbamazepine includes a boxed warning stating that HLA-B*1502 genetic testing should be performed prior to initiating carbamazepine therapy to identify Asian individuals at increased risk for significant cutaneous adverse drug reactions. As a rule, carbamazepine should not be used in individuals positive for HLA-B*1502. Individuals who test negative for the allele have a low risk of SJS/TEN, but should undergo routine monitoring for toxicity.

### Criteria

HLA-B*1502 variant testing is indicated in individuals with Asian ancestry prior to initiation of or during the first nine months of treatment with carbamazepine therapy.

### References

**HLA-B*5701**

<table>
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<tr>
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<td>HLA-B*5701 testing for abacavir toxicity</td>
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**Description**

Abacavir (Ziagen®, Epzicom®, Trizivir®) is an antiretroviral agent used in the treatment of human immunodeficiency virus type 1 (HIV-1). About 5-8% of individuals have an immunologically-mediated hypersensitivity reaction (HSR) while on treatment and are not able to tolerate abacavir. The abacavir HSR includes a combination of rash, fever, GI symptoms (such as nausea, vomiting, diarrhea, or abdominal cramping), constitutional symptoms (tachycardia, hypotension, myalgia, fatigue, pain, malaise, dizziness and headache), and respiratory symptoms. The hypersensitivity reaction to abacavir is strongly associated with the presence of the major histocompatibility complex class I allele HLA-B*5701. Individuals with a positive HLA-B*5701 test are at risk for abacavir HSR. Not all HLA-B*5701 carriers will have immunologic-confirmed HSR. Product labeling for abacavir containing drugs includes a boxed warning stating that these drugs should be avoided in individuals who test positive for HLA-B*5701.

**Criteria**

HLA-B*5701 testing is indicated in individuals with HIV-1 prior to the initiation of any abacavir-containing therapy.

**References**

Huntington Disease

<table>
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<tr>
<th>Procedure covered by this policy:</th>
<th>Procedure Code(s)</th>
<th>Requires:</th>
<th>Lab Procedure Restrictions†</th>
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<tr>
<td>Targeted mutation analysis for CAG trinucleotide repeat expansion in HTT</td>
<td>81401</td>
<td>Yes</td>
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</table>

* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specific sequence to be followed or additional information is required and must be supplied by the lab performing procedure(s) for full claim payment.

Description

Huntington Disease (HD) is an inherited condition characterized by a progressive movement disorder, cognitive decline and psychiatric disturbances. The condition generally affects individuals between 35-45 years of age, but has been diagnosed in young children and elderly adults. On average, the progression of the disease occurs over 15 years, with an average age of death around age 55.

One gene, HTT, is associated with HD, which is caused by a CAG trinucleotide repeat. The number of CAG DNA repeats varies among individuals and can be classified into three groups, depending on the number of repeats: unaffected, intermediate, and full mutation (affected status). The typical HTT gene has <26 repeats. An HTT gene with 27-35 repeats is considered an intermediate size, and is seen in approximately 1-5% of the Caucasian population. Carriers of an intermediate allele typically do not have symptoms of HD. However, when this allele is passed on to future generations by a male the expansion can increase. This is seen more frequently when the male parent is of advanced paternal age. To date, there has not been a documented case of maternal transmission of an expanded allele, although there remains a theoretical risk for this fact. A full mutation range is greater than or equal to 36 repeats. Full mutations can be further classified as reduced penetrance and full penetrance. Individual with 36-39 repeats may or may not develop symptoms. Many individuals either will not develop symptoms or develop symptoms at an elderly age. As the repeat lengths increase, the rate of symptoms occurs at an earlier age. A mutation of 40 repeats or greater is consistently associated with the development of HD symptoms. Individuals with repeats >60 have very early onset of symptoms, which can occur under the age of 18. It is estimated that 5-10 in 100,000 Caucasian individuals are affected with HD. The prevalence seems to be lower in Japan, China, Finland and African blacks, with an estimated frequency in Japan being 0.1-0.38 per 100,000.

Diagnosis of HD occurs through targeted mutation analysis, using either PCR or Southern Blot technology. The use of PCR or Southern blot will be determined on the size of the expanded allele. Targeted mutation analysis can detect 100% of all cases. Once a deleterious mutation has been identified, relatives of affected individuals can be tested. Prenatal testing is available to individuals with a known family mutation. Genetic testing can be performed on amniocytes obtained through amniocentesis or chorionic villi obtained through chorionic villus sampling.

HD is inherited in an autosomal dominant inheritance pattern. In autosomal dominant conditions, the disease is typically seen in every generation. This means that an individual with a CAG expansion has a 50% chance of passing it on to their children, although with HD having intermediate alleles and penetrance...
based on the number of CAG repeats, an individual may not become symptomatic. Depending on the allele size, the disease may look to occur as a de novo mutation. When the allele is passed onto each generation, a phenomenon called anticipation is seen. This means that the gene will expand as it is passed to each generation. The larger the size of the allele, the gender and age of the transmitting parent, and whether the CAG repeat is interrupted with other DNA trinucleotide segments will determine how likely it is to pass on a full expansion. In HD, the allele tends to expand more quickly when it is passed from father to child than from mother to child.

Several phenocopies have been reported, but have a much lower incidence in the population. A phenocopy is defined as a condition that has a phenotype that is identical to another condition. Because of the identical nature of the disease, several of the phenocopies have been named “Huntington-Like” or HDL. The phenocopies include: Huntington disease-like (HDL1), HDL2, HDL3, spinocerebellar ataxia (SCA17) 17 (HDL4), SCA 1/2/3, DentatoRubral-Pallodolysian syndrome (DRPLA), and others.

Preventive use of genetic testing on a population wide basis, for any condition, may be cost-effective if genotypic information can be shown to predict disease risk. Population-wide screening is ethically justifiable only if there is an efficacious and cost-effective intervention to prevent the disorder in those who are identified as being at increased risk. Despite that the DNA test is very accurate, it is important to ensure that effective means are in place to adequately counsel tested populations about the meaning and implications of the results. The nature of different phenotypes as a result of the gene expansion is complex. At this time, population wide carrier screening for HD syndrome is not recommended.

The National Society of Genetic Counselors (NSGC) advocates genetic counseling for individuals and families who are undergoing genetic testing. Genetic testing to determine carrier status or confirm a diagnosis is important for reproductive information and medical management of symptoms. The American Society of Human Genetics/American College of Medical Genetics (ASHG/ACMG) also agrees that genetic testing in children for adult onset conditions should occur under specific circumstances where psychological, medical and reproductive benefits are apparent for the individual being tested.

As a result of the above guidelines, genetic testing should be approved to confirm a diagnosis or carrier status in anyone who meets clinical criteria for HD. Additionally, genetic testing should be approved to determine the carrier status in an at risk relative with a known family mutation. Individuals who meet clinical criteria for HD testing should be offered targeted mutation analysis. Finally, individuals with a family history of a known CAG expansion should be offered testing.

Once a CAG expansion has been identified, surveillance should begin for HD symptoms. Affected individuals should receive supportive assistance to help maximize potential. At this time, there is no treatment that will delay or stop the onset of symptoms. Individuals identified as presymptomatic, should begin to put in place the plans for future care. Individuals with symptoms should receive supportive care, with attention to nursing, diet, special equipment and eligibility for state and federal benefits. Numerous social problems affect individuals with HD and their families, and therefore practical help, emotional support and counseling can provide some respite.

Other References 4,6,9-18
Criteria

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

- Clinical Consultation:
  - Genetic counseling - pre and post-test counseling by a medical geneticist or genetic counselor, and
  - Examination by a geneticist or physician familiar with genetic movement disorders, AND
- Previous Genetic Testing:
  - No previous genetic testing of HTT, AND
- Diagnostic Testing for Symptomatic Individuals:
  - For individuals ≥18 years: (at least 2 of the following)
    - Progressive motor disability featuring involuntary movements (chorea) and gait disturbance, and/or
    - Behavioral disturbances including:
      - Personality change
      - Depression
      - Cognitive decline, and/or
    - Family History of Huntington's Disease
  - For individuals ≤17 years: (at least 2 of the following)
    - Progressive motor disability featuring involuntary movements (chorea) and gait disturbance, and/or
    - Cognitive decline, and/or
    - Stiffness or rigidity, and/or
    - Epilepsy/myoclonus and tremor, and/or
    - Family History of Huntington's disease, OR
- Predictive Testing for Presymptomatic/Asymptomatic At-Risk Individuals*:
  - Known CAG trinucleotide repeat expansion in HTT in 1st, 2nd, or 3rd degree biologic relative, or
  - One or more 1st degree biologic relative(s) with clinical diagnosis of HD and mutation unknown/not yet tested, or
  - 18 or older, OR

*Includes prenatal testing for at-risk pregnancies.

References


## Hypertrophic Cardiomyopathy

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<td>Molecular pathology procedure, Level 8, full gene sequence MYBPC3</td>
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<td>Molecular pathology procedure, Level 8, full gene sequence MYH7</td>
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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specific sequence to be followed or additional information is required and must be supplied by the lab performing procedure(s) for full claim payment.

[Click here for applicable Medicare NCD/LCD information](#)

### Description

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant inherited disorder of the heart muscle characterized by left ventricular hypertrophy (LVH). This unexplained thickening of the heart muscle interferes with the heart's function by reducing blood flow into and out of the heart chambers. The clinical manifestations of HCM can range from a benign course with minimal, if any, symptoms, to progressive disease and the development of heart failure, to sudden cardiac death (SCD), which can be the first sign of the disease. HCM is the most common inherited cardiovascular condition in the U.S. The incidence is 1 in 500 individuals and over 90% of cases are familial. LVH usually develops during adolescence or young adulthood, although this can vary. HCM has been reported in infants and young children, but it can develop later in life. The clinical manifestations of HCM vary depending on the mutation and which genes.
Hypertrophic Cardiomyopathy

are involved. Different mutations in the same gene can result in a high risk of SCD, while other mutations do not adversely affect a patient's health or life.\(^4,5,6\) The clinical symptomatology also appears to be influenced by gender and the presence of polymorphisms in other genes.\(^7\)

Molecular genetic studies have defined HCM as a disease of the sarcomere; the basic contractile unit within the cardiac myocyte composed of a number of different protein structures including thick and thin filaments.\(^1\) It is defined clinically by the presence of LVH, as measured by echocardiography or MRI, in the absence of other known causes.\(^3,10\) This is a diagnosis of exclusion. People with LVH must be examined thoroughly for the presence of other cardiac disorders that can lead to hypertrophy such as valvular disease, long-standing hypertension, or other myocardial diseases before the diagnosis of HCM can be established.\(^3\) Other inherited syndromes, as well as metabolic and mitochondrial disorders must also be excluded as an underlying cause of HCM.\(^1,11\) These include infiltrative disorders like amyloidosis, and sarcoidosis, neuromuscular diseases like Noonan syndrome and Friederich ataxia, and glycogen storage diseases including Pompe disease and Fabry disease, which may account for up to 5% of cases of HCM in adults.\(^11\) It is especially important to rule out Fabry disease as this is a treatable condition.\(^11\)

The clinical presentation typically includes chest pain, palpitations, exertion-related dyspnea, and/or impaired consciousness.\(^3,11,12\) However, the majority of individuals with HCM are asymptomatic and are only discovered when being worked up for an incidental finding such as a heart murmur.\(^11,12\) Others experience symptoms of progressive exercise intolerance and heart failure, or unexpected SCD.\(^3,13\) HCM leads to death in about 10% to 20% of patients.\(^3,14\) Of the 744 patients with HCM in a study by Maron et al., 6% died from SCD (mean age 45 years), 4% from congestive heart failure, (mean age 56 years), and 2% from stroke (mean age 63 years).\(^14\)

HCM is the most common cause of SCD in teens and adults under age 35, and accounts for approximately one-third of all SCD in athletes.\(^12,13,15\) The current annual frequencies of HCM-related sudden death are approximately 1-2% in children and adolescents, and 0.5-1% in adults.\(^13,16\) Children who are genetically predisposed to HCM may be advised not to participate in certain competitive sports for this reason.\(^17\) Extensive cardiac screening at regular intervals can identify patients at high risk for SCD, who may benefit from implantation of a cardioverter-defibrillator (ICD), which in one study corrected potentially lethal arrhythmias in 20% of the 506 high-risk HCM patients, or other interventions.\(^18\)

Mutations in one or more of the sarcomere contractile protein genes have been found in approximately 40 to 60% individuals with HCM.\(^11\) However, the penetrance is incomplete and can vary even within families. Charron et al. (1996) evaluated 90 individuals in 10 families with documented HCM and found that 69% had electrocardiographic (ECG) and/or echocardiographic evidence of HCM.\(^4\) In 2009, Michels et al. diagnosed HCM in 31 of 76 (41%) asymptomatic mutation carriers.\(^5\) Disease penetrance was more common in men than woman. Penetration was higher in patients with MYH7 gene mutations than in patients with mutations in the MYBPC3 gene (60% vs. 36%). They also observed that relatives without any ECG or echocardiographic criteria were significantly younger than the carriers diagnosed with HCM, suggesting an age dependent disease penetrance.\(^5\) Christiaans et al. examined 235 asymptomatic mutation carriers from 83 families with a known pathogenic MYBPC3 mutation and found evidence of HCM in 22.6% of their patients.\(^6\) The majority of mutation carriers were diagnosed with HCM after the age of 50, and 11% had other risk factors that increased their risk for SCD. Like Michels et al., this group also concluded that their data justified predictive DNA testing in HCM families with a pathogenic mutation and regular cardiologic evaluations until "advanced age."\(^5,6\)
In addition to age, gender, and genetic mutations, potential genetic modifying factors have also been discovered. For example, homozygosity for the angiotensin-converting enzyme (ACE) deletion allele polymorphism is more common in patients from HCM families with a high incidence of sudden death. This may be due to the fact that DD homozygotes are at increased risk for hypertension.

More than 450 different mutations have been identified within 13 sarcomere and myofilament-related genes. Genetic analyses of a subset of these sarcomeric genes in families and patients with unexplained LVH have resulted in the identification of mutations in 33% to 63% of cases. In the majority of cases, the disease is due to a single pathologic mutation, although in rare cases multiple pathologic mutations have been identified.

The majority of mutations in the sarcomeric genes are missense mutations with amino acid substitutions. However, insertions, deletions, and splice site mutations encoding for truncated sarcomeric proteins have also been described. Mutations in the beta-myosin heavy chain (MYH7) and myosin-building protein C (MYBPC3) genes account for the majority of identified mutations. More than 50 different mutations have been found in the MYH7 gene, and account for approximately 15% to 44% of adult cases. Mutations in the MYBPC3 gene have been found in approximately 15% to 35% of patients, especially in patients with late-onset HCM, in whom ECG or echocardiographic features of HCM may not always appear before the age of 40.

<table>
<thead>
<tr>
<th>Encoded Protein</th>
<th>Gene Symbol</th>
<th>Sarcomere Component</th>
<th>Percentage of all cases</th>
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</thead>
<tbody>
<tr>
<td>β-Myosin heavy chain</td>
<td>MYH7</td>
<td>Thick filament</td>
<td>15-44</td>
</tr>
<tr>
<td>Myosin-binding protein C</td>
<td>MYBPC3</td>
<td>Thick filament</td>
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<td>TPM1</td>
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<td>Thick filament</td>
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<tr>
<td>Titin</td>
<td>TTN</td>
<td>Thick filament/Z-Disc</td>
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<tr>
<td>LIM binding domain 3 (alias ZASP)</td>
<td>LBD3</td>
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<td>1-5b</td>
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<td>Muscle LIM protein</td>
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<tr>
<td>Vinculin</td>
<td>VCL</td>
<td>Intercalated disc</td>
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</table>

The Z-disc is a framework of proteins that connect the sarcomere units to each other. Analyses of Z-disc proteins have revealed mutations in some of these proteins as additional rare causes of HCM. Z-disc protein mutations implicated in the pathogenesis of HCM have been identified in LIM binding domain 3 (LBD3), muscle LIM protein (CSRP), encoded telethonin (TCAP), myozenin 2 (MYOZ2). Mutations in the vinculin gene (VCL), which encodes a cytoskeletal protein that anchors the thin filaments to the intercalated discs and nexilin encoded by NEXN, have also been described.

In addition, molecular genetic studies have defined several mutations in genes that do not encode sarcomeric proteins in approximately 5% of patients with unexplained cardiac hypertrophy. For example, missense mutations in the gene encoding the gamma-2-regulatory subunit of the AMP-activated protein kinase (PRKAG2) have been reported to cause familial LVH associated with ventricular pre-excitation. Individuals with mutations in the PRKAG2 gene can be distinguished from those with typical sarcomere protein gene mutations by the absence of myocyte disarray (i.e., one of the histopathologic features that is characteristic of HCM), progressive conduction system disease with heart block, and the accumulation of glycogen in the myocytes. Mutations in the lysosomal-associated membrane protein 2 (LAMP2) and alpha-galactosidase (GLA) can also cause glycogen storage diseases that present as unexplained HCM.

About 10% of cases of HCM are nonfamilial (sporadic), but a portion of these individuals with apparent sporadic HCM have sarcomeric protein gene mutations. Potential explanations for this finding include reduced penetrance, unrecognized disease in relatives, nonpaternity, unknown adoptive status, and de novo mutations. The actual rate of de novo mutations is unknown.

Commercial testing for HCM typically includes an analyses of all of the genes encoding different components of the sarcomere. Some commercial laboratories are also testing for mutations in troponin C (TNNC1), and genes involved in the glycogen storage diseases (PRKAG2, LAMP2, GLA), mitochondrial disorders (MTTG, MTTI, MTTK, and MTTQ), amyloidosis (TTR), and one form of muscular dystrophy (CAV3). No definitive genotype-phenotype correlations can be used to direct the approach to testing. If there is no known familial mutation, comprehensive mutation analysis is the method of choice. By testing a patient with established disease, the predictive value of testing at-risk relatives is improved if a genetic mutation is found in the index patient. The improved predictive value leads to the ability to rule out an inherited predisposition to HCM with near certainty in relatives who test negative for the familial mutation. Given that close to 40% of people with unexplained HCM do not have an identifiable gene mutation it is not possible to rule out an inherited familial predisposition for HCM if a pathogenic mutation is not found in the index patient. In these cases, the relatives of the index patient are still at risk for the development of HCM and clinical surveillance should continue. Relatives who do not have the mutation can continue screening for HCM and will not have to consider modifying their lifestyle or changing their reproductive plans. Prenatal diagnosis for familial HCM is possible if the disease causing mutation is known. Prenatal diagnosis can be accomplished by analyzing fetal DNA extracted from cells obtained through CVS or amniocentesis. Individuals who carry a pathogenic mutation can also consider the option of preimplantation genetic diagnosis.
Clinical surveillance for signs of HCM should continue for at-risk individuals who test positive for a familial mutation. They should also be counseled about their lifestyle, career choice and reproductive options. Because of the risk of sudden death, it is important for people with HCM to avoid too much strenuous activity and intense exercise. Prolonged activity in hot weather is not recommended, because dehydration can also worsen symptoms.

Criteria

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

**Known Family Mutation(s) for Hypertrophic Cardiomyopathy**

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist, genetic counselor, or cardiologist, or other specialist as deemed by Health Plan policy, AND
- Previous Genetic Testing:
  - No previous HCM-associated genetic testing, AND
- Diagnostic/Predisposition Testing for Presymptomatic/Asymptomatic Individuals*:
  - HCM known family mutation in 1st degree biologic relative, AND
  - Rendering Laboratory is a qualified provider of service per Health Plan policy.

*NOTE: Since symptoms may occur in childhood, testing of children who are at-risk for a pathogenic mutation may be appropriate, but requires genetic counseling and careful consideration of ethical issues related to genetic testing in minors.3

**Hypertrophic Cardiomyopathy Genetic Testing Panel**

**Note:** Gene panels specific to HCM will be paid according to the criteria outlined in this policy. Pan-cardiomyopathy panels which include genes for HCM, as well as other conditions, such as dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), left ventricular noncompaction (LVNC), and catecholaminergic polymorphic ventricular tachycardia (CPVT) are not eligible for coverage.

- Genetic Counseling & Medical Consultation:
  - Pre and post-test counseling by a medical geneticist, genetic counselor, or cardiologist, or other specialist as deemed by Health Plan policy, and
  - Assessment by a cardiologist familiar with hereditary causes of HCM, AND
- Previous Testing:
  - No previous genetic testing for HCM, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Echocardiogram demonstrating LVH without obvious cause (valvular disease, hypertension, infiltrative or neuromuscular disorder), and
  - Myocardial wall thickening of greater than or equal to 15mm (1.5cm), or
  - Presence of pathognomonic histopathologic features of HCM
    - Myocyte disarray
    - Hypertrophy
    - Increased myocardial fibrosis, and
The results of the test will directly impact the diagnostic and treatment options that are recommended for the patient, and

After genetic counseling, pedigree analysis, physical exam, and conventional diagnostic studies, a definitive diagnosis of HCM remains unclear, OR

- Predisposition Testing for Presymptomatic/Asymptomatic Individuals*:
  - 1st degree relative with a diagnosis of hypertrophic cardiomyopathy and known mutation—see section 1-A.
  - If no known mutation in an affected 1st or 2nd degree relative, see section V, OR

- Rendering Laboratory is a qualified provider of service per Health Plan policy.

<table>
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<tr>
<th>NCD/LCD Jurisdiction and CPT Codes</th>
<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
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References

KRAS Testing, Anti-EGFR Treatment Response

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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

*Click here for applicable Medicare NCD/LCD information*

**Description**

Cetuximab (Erbitux®) and panitumumab (Vectibix®) are cancer chemotherapy drugs specifically targeted to human epidermal growth factor receptor (anti-EGFR) that are used in the treatment of advanced colorectal cancer. Tumors with a mutation in the KRAS gene will not respond to anti-EGFR therapy. Colon cancer treatment guidelines from the National Comprehensive Care Network recommend KRAS testing prior to initiation of anti-EGFR therapy.

**Criteria**

KRAS mutation testing is indicated in individuals with metastatic colorectal cancer prior to the initiation of treatment with cetuximab (Erbitux®) or panitumumab (Vectibix®) therapy.

**NCD/LCD Jurisdiction and CPT Codes**

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**KRAS Testing, Anti-EGFR Treatment Response**

AR, LA, MS, CO, NM, OK, TX

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AZ, MT, ND, UT, WY, SD, ID, AK, WA, OR

LCD: L24308 (http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=24308&ContrId=359&ver=73&ContrVer=1&Date=&DocID=L24308&SearchType=Advanced&bc=KAAAAAgAAAAAAA%3d%3d&)

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<td>Yes (Group 2)</td>
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81479 UNLISTED MOLECULAR PATHOLOGY

Therascreen KRAS

Yes  No  Yes

DE, DC, MD, NJ, PA

81275 KRAS GENE

Yes  Yes  No

FL, PR, VI


81275 KRAS GENE

No  No  No

VA, NC, SC, WV

81479 UNLISTED MOLECULAR PATHOLOGY

Therascreen KRAS

Yes  No  Yes

See LCD jurisdictions that refer to MolDX.

81275 KRAS GENE

No  No  N/A

81403 MOPATH PROCEDURE LEVEL 4

KRAS analysis exon 3

Yes  No  N/A

81405 MOPATH PROCEDURE LEVEL 6

KRAS full gene sequencing

Yes  No  N/A

81479 UNLISTED MOLECULAR PATHOLOGY

Qiagen Therascreen KRAS Kit

Yes  No  N/A

References

## Li-Fraumeni Syndrome

<table>
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<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Procedure Code(s)</th>
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<th>Prior-authorization* Requirement</th>
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<td>TP53 Full Sequence Analysis</td>
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† - Lab procedures require specific sequence to be followed or additional information is required and must be supplied by the lab performing procedure(s) for full claim payment.

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### Description

Li-Fraumeni Syndrome (LFS) is a cancer predisposition syndrome that is associated with multiple primary cancers and sarcomas. This includes soft tissue sarcoma, osteosarcoma, leukemia, melanoma, and cancer of the breast, pancreas, colon, adrenal cortex, stomach, esophagus and brain. Overall, greater than 75% of individuals with LFS develop cancer, compared with 10% in the general population. It is estimated that of those with an initial primary tumor, approximately 15% will develop a second primary tumor, 4% will develop a third and 2% will develop a fourth primary tumor.

Two forms of LFS are recognized, classic LFS and Li-Fraumeni-like (LFL) syndrome. Classic LFS syndrome has been defined as an individual with a sarcoma under the age of 45 having a first degree relative under 45 with any cancer and another first or second degree relative under 45 on the same side of the family with a cancer or a sarcoma at any age. This criteria, however, does not identify many of the LFL families. LFL shares some of the features of LFS and cancers may occur at later ages. Therefore, several groups have relaxed criteria in order to include families that may have the syndrome.

Although individuals with LFS often live to adulthood, they are at an increased risk for early death as a result of cancer. In young adults, premenopausal breast cancer is the greatest risk. It is estimated that 57% of individuals with LFS will develop cancer by the age of 30. In LFL families, 44% were diagnosed by age 30 and 78% were diagnosed by age 50. It is estimated that TP53 mutations make up 2-10% of childhood brain cancers, 50-100% of childhood adrenocortical carcinomas, 2-3% of osteosarcomas, and 9% of rhabdomyosarcomas and 7-20% of primary tumors occurring at early ages.

The gene TP53 is associated with most cases of LFS and LFL. Approximately 70% of families with classic LFS have a mutation in TP53, where 8-22% of individuals with LFL syndrome have an identifiable TP53 mutation. More than 250 mutations have been found in this gene, with some genotype/phenotype observations noted. Specifically, frameshift mutations have been associated with higher cancer risks and certain missense mutations have been associated with lower cancer risks.

LFS is a rare cancer syndrome and is inherited in an autosomal dominant pattern. In autosomal dominant conditions, the disease is typically seen in every generation. This means that an individual has a 50% chance of passing on a mutation to their children. Additionally, parents, siblings and children of known carriers have a 50% chance of being carriers of the same mutation. However, the risk to siblings does
depend on whether the parents of an affected individual have the same TP53 mutation. While most mutations are inherited, de novo germline mutations have been reported. The frequency of de novo mutations has not been established; however in one study 4 of 17 mutations were reported as de novo.15 Siblings of individuals with a de novo mutation have a low (but not zero) risk of carrying a mutation.

Diagnosis of LFS can occur through targeted mutation analysis of the TP53 gene, sequence analysis of the TP53 gene or deletion analysis of the TP53 gene. Targeted mutation analysis is available for individuals with a known familial mutation. Sequence analysis can identify ~95% of mutations. TP53 deletions are not common, but have been reported.13 Once a deleterious mutation has been identified, relatives of affected individuals can be tested. Genetic testing should be offered to at-risk family members in a family where a germline TP53 mutation has been identified. This includes testing the parents of children who have an identified mutation. At this time, population wide carrier screening for LFS is not recommended.4

Recommendations on the genetic testing for TP53 mutations were made in 1992. These recommendations include: genetic counseling for individuals undergoing genetic testing, testing at risk family members for TP53 mutations, advise against population-based testing for TP53 mutations and establishing long-term follow up for individuals identified with a mutation.4,20 The American Society of Clinical Oncology policy statement emphasizes genetic counseling be conducted prior to genetic testing, patients be well informed about pros and cons prior to testing, access to testing be equal to all, and test results be kept private and confidential.16

As a result of the above recommendations genetic testing is approved to confirm a diagnosis or predisposition to the disease in anyone who meets clinical criteria for LFS. Individuals that meet clinical criteria for LFS testing should be offered sequence analysis. Deletion/duplication testing should be offered to those who meet the criteria and have tested negative through sequence analysis. Additionally, genetic testing should be approved to determine the status in an at risk relative with a known family mutation. If the known mutation is not detected, sequencing should follow in the rare circumstance of a strong family history on the opposite side of the known family mutation. If an LFS diagnosis is made, treatment changes and increased screening should be in accordance with the published care guidelines.7,17

### Core Cancers – 80% of LFS Cancers18
- Sarcomas
- Breast cancer (premenopausal)
- Brain tumors
- Adrenocortical carcinomas

### Additional Cancers – 20% of LFS Cancers
- Colorectal cancer
- Prostate Cancer
- Lung cancer
- Stomach Cancer
- Endometrial cancer
- Thyroid Cancer
- Esophageal cancer
- Gonadal germ cell tumor
- Neuroblastoma
- Ovarian cancer
- Pancreatic cancer
- Hematopoietic malignancies (leukemias and lymphomas)
- Wilms’ tumor and other kidney cancers
- Melanoma and non-melanoma skin cancer

### Criteria
Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.
Known TP53 Family Mutation Testing

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist or genetic counselor, AND
- Previous Testing:
  - No previous genetic testing of TP53, AND
- Diagnostic and Predisposition Testing for Presymptomatic/Asymptomatic Individuals*:
  - Known family mutation in TP53

* Includes prenatal testing for at-risk pregnancies.

Full Sequence Analysis of TP53

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist or genetic counselor. 2, 5, AND
- Previous Testing:
  - No previous sequencing of TP53, and
  - No previous duplication/deletion analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Li-Fraumeni Syndrome – Chompret Criteria 2009:
    - Multiple primary tumors, two of which must be LFS spectrum tumors (sarcoma (not Ewing sarcoma), pre-menopausal breast cancer, brain tumor (non meningioma), adrenocortical carcinoma, leukemia, or lung bronchoalveolar cancer) with the initial diagnosis ≤ 45, or
    - Diagnosis of adrenocortical carcinoma (ACC) or choroid plexus tumor at any age, or
    - LFS spectrum tumor diagnosis at ≤ 45 years of age and
      - 1st or 2nd degree biologic relative diagnosed with LFS spectrum tumor before the age of 56 (except breast cancer if proband has breast cancer) and
      - or with multiple tumors as above (i) at any age, OR
  - Li-Fraumeni-Like Syndrome – Birch Criteria:
    - LFS spectrum tumor diagnosis at ≤ 45 years of age, and
    - 1st or 2nd degree biologic relative diagnosed with LFS spectrum tumor at any age, or
    - A second 1st or 2nd degree relative with any cancer diagnosed < 60 years of age, OR
  - Premenopausal (<36) breast cancer if BRCA1 and 2 testing is negative (NCCN guideline), OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - One or more biologic relatives (1st, 2nd, or 3rd degree) with a clinical diagnosis of LFS/LFL (according to a or b or c above) and no known family mutation or no testing to date, OR
Deletion/Duplication Analysis of TP53

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist or genetic counselor. 2, 5, AND
- Previous Testing:
  - No previous deletion analyses of TP53, and
  - No mutation detected on full sequencing of TP53.

† Lab Testing Restriction: Deletion/Duplication Analysis of TP53 is authorized if no mutation is detected on full sequencing of TP53.

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<th>NCD/LCD Jurisdiction and CPT Codes</th>
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References


**Long QT Syndrome**

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<th>Procedure Code(s)</th>
<th>Requires:</th>
<th>Prior-authorization*</th>
<th>Lab Procedure Restrictions†</th>
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</table>

* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Click here for applicable Medicare NCD/LCD information

### Description

Inherited channelopathies are characterized by changes within the action potential function, resulting in atypical functioning of calcium or sodium-ion channels within the heart's electrical system. The result of this atypical functioning includes syncope (fainting) events, arrhythmias, “seizures”, and sudden death in the young. There are a variety of different channelopathies with known disease causing associated genes ranging from <20% - 75%. Therefore, a negative test can never rule out disease in an individual, whereas a positive test can confirm a diagnosis and provide information for at-risk relatives. This policy will focus on one channelopathy – Long QT syndrome (LQTS).

Long QT Syndrome (LQTS) is characterized by a prolonged QT wave, with T wave and U wave abnormalities. The majority of individuals will have prolongation of their QT interval at rest on a 12-lead electrocardiogram (ECG); however, 10-40% of individuals will have a normal QT interval at rest. Therefore, exercise testing, catecholamine stress testing or holter monitoring may be needed to document QT abnormalities. LQTS can be congenital or acquired. Several medications can cause acquired LQTS including antifungal and antimicrobial medications, class 1A antiarrhythmic agents and class III antiarrhythmic agents, as well as others. The best characterized congenital forms of LQTS include the Jervell and Lange-Nielsen and Romano-Ward syndrome (RWS).

The diagnosis of RWS is based on ECG results, clinical presentation and family history. ECG results differ based on gender. As not everyone with RWS has a prolonged QT interval at rest, QT is also measured during exercise or ambulatory ECG as well as during pharmacologic provocation testing. In addition to QT abnormalities, other abnormalities can be present including T wave patterns or ventricular fibrillation. A personal history of fainting spells or aborted cardiac arrest can help identify those at risk for RWS. A family history of syncope, aborted cardiac arrest or sudden cardiac death, especially in an autosomal dominant inheritance pattern, increases the risk for LQTS. Prior to the availability of genetic testing, a scoring system was used to diagnose an individual with disease. Points are given based on the ECG results, personal syncope history and family history. An individual with 0 points has a low probability of RWS, whereas 0.5-3.0 has an intermediate probability, and ≥3.5 has a high probability of RWS. RWS has been associated with thirteen different genes and >800 allelic mutations. Approximately 25% of RWS families do not test positive for a mutation in one of the 10 known genes, suggesting that there are...
other genes that have not been identified.\textsuperscript{4} Three genes – \textit{KCNQ1} (LQTS1), \textit{KCNH2} (LQTS2), and \textit{SCN5A} (LQTS3) – consist of the majority of RWS cases (46\%, 38\% and 13\%, respectively). Phenotypes associated with mutations in these genes include a cardiac event resulting from exercise and sudden emotion, exercise, emotion and sleep, and sleep only, respectively. At least half of individuals with a disease-causing mutation do not have symptoms, and those that do have syncope symptoms can range from one event to hundreds – with an average of just a few.\textsuperscript{7}

Cardiac events may occur from infancy through middle age, but are most common in the pre-teen years through the 20s.\textsuperscript{4} The most common are syncope events; however, these events occur differently based on the genotype. Syncope events are seen most frequently in LQTS1 (63\%), followed by LQTS2 (46\%) and LQTS3 (18\%), whereas life-threatening events are seen more frequently in LQTS3.\textsuperscript{8}

RWS is inherited in an autosomal dominant inheritance pattern, found in approximately 1 in 3,000.\textsuperscript{4} A founder effect has been suggested in the state of Utah and Finland, with a prevalence around 1 in 5,000 (Piippo 2001). Some evidence suggests that there is a lower prevalence in Africans.\textsuperscript{4} In autosomal dominant conditions, the disease is typically seen in every generation. This means that an individual has a 50\% chance of passing on a mutation to their children. Additionally, parents and siblings of known carriers have a 50\% chance of being carriers of the same mutation. When a mutation in a child is not found in the parent, it is assumed that there is a \textit{denovo} mutation in the child, or the parent has a germline mutation. Sibs would still need to be tested to rule out germline mutations.

The presence of symptoms for RWS is age related with most people exhibiting symptoms starting in the pre-teens through the 20s.\textsuperscript{6} Therefore, testing individuals under the age of 18 in families where LQTS is suspected or known is standard practice. A DNA test for RWS should be offered to the person who has the most obvious disease, as that individual will more likely test positive than someone without disease.\textsuperscript{9} At this time, population wide carrier screening for RWS is not recommended.\textsuperscript{2}

The diagnosis of Jervell and Lange-Neilsen syndrome (JLNS) is characterized by congenital, bilateral profound deafness and long QT interval.\textsuperscript{3,4} The classic presentation of a JLNS a deaf child who has had a syncopal event after exercise, is under stress or had a fright. It is estimated that 50\% of children with JLNS will have a fainting spell by the age of 3, with emotion being the primary trigger.\textsuperscript{10}

Two genes, \textit{KCNQ1} or \textit{KCNE1}, are associated with JLNS. \textit{KCNQ1} is associated with approximately 90\% of mutations in this condition,\textsuperscript{11} whereas \textit{KCNE1} is associated with up to 10\%.\textsuperscript{10} Genotype-phenotype associations have been noticed, with mutations in \textit{KCNE1} having a milder presentation.

JLNS is inherited in an autosomal recessive inheritance pattern. The prevalence of JLNS varies, depending on the population. It is estimated that 1 in 10,000 individuals in Norway are affected with JLNS, and one study found that about 1 in 175 individuals in a deaf population are affected with JLNS. Populations where consanguinity is more prevalent have a higher risk of having a child with JLNS. Parents of an affected child most likely each carry a copy of a mutation, however, in rare cases only one parent will carry a mutation and the other mutation is \textit{denovo}. Siblings of affected individuals have a 25\% chance of being affected, and a 50\% chance of being a carrier for JLNS. In some cases, individuals who are heterozygous for a JLNS mutation can have long QT symptoms, but do not have deafness. These individuals would then be followed as though they have RWS. Most affected individuals are compound heterozygotes, meaning that they have two different mutations causing their LQTS.
Diagnosis of RWS can occur through sequence analysis and deletion analysis of the commonly affected genes, \textit{KCNQ1} (LQTS1), \textit{KCNH2} (LQTS2), and \textit{SCN5A} (LQTS3). Once a deleterious mutation has been identified, relatives of affected individuals can be tested. Genetic testing should be offered to at-risk family members in a family where a RWS mutation has been identified. Early detection of at-risk individuals affects medical management. Although prenatal testing is available to individuals with a known family mutation, it is not often used.

Two independent reviews found that genetic testing has significant diagnostic value for LQTS, including testing of asymptomatic individuals.\textsuperscript{12} Consensus reports from the US National Heart, Lung and Blood Institute\textsuperscript{13}, the office of Rare Diseases, Heart Rhythm Society (HRS)/European Heart Rhythm Association\textsuperscript{2}, and the Heart Rhythm UK Familial sudden Death syndromes Statement Development group\textsuperscript{14} suggest that genetic testing for LQTS should be combined with a clinical evaluation.\textsuperscript{6}

The scientific framework that has been proposed to evaluate genetic discoveries is “ACCE”: analytic validity, clinical validity, clinical utility and ethical, legal, and social implications.\textsuperscript{15} Analytic validity has been found to be >95%.\textsuperscript{16-18} Genetic analysis has been found useful to provide risk stratification of LQTS patients, and identify at-risk relatives.

As a result of the above guidelines, genetic testing should be approved to confirm a diagnosis or predisposition in anyone who meets clinical criteria for RWS. Additionally, genetic testing should be approved to determine the genetic status in an at-risk relative with a known family mutation. Individuals who have a family member with a known LQTS mutation(s) should be tested for that/those mutation(s). Individuals who meet clinical criteria for LQTS testing should be offered sequence analysis. MLPA testing should be offered to those who meet the criteria and sequence analysis failed to detect a mutation. Finally, individuals with a known family mutation in a LQTS gene should be offered targeted testing for the family mutation only. If no family mutation is found, they should only go on to sequencing if their family history suggests that this is necessary (i.e. a strong family history on the opposite side from the known family mutation).

**Guidelines and Evidence**

A 2011 expert consensus statement from the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) recommends:\textsuperscript{2}

- “Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient’s clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype.”\textsuperscript{2}
- “Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc>480ms (prepuberty) or >500ms (adults).”\textsuperscript{2}
- “Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values>460ms (prepuberty) or >480ms (adults) on serial 12-lead ECGs.”\textsuperscript{2}
Mutation specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.\textsuperscript{2}

Criteria

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

**Known Family Mutation for Long QT Syndrome**

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing for Long QT Syndrome, AND
- Diagnostic and Predisposition Testing:
  - Long QT Syndrome family mutation identified in 1st degree relative(s). (Note: 2nd or 3rd degree relatives may be considered when 1st degree relatives are unavailable or unwilling to be tested), AND
- Rendering Laboratory is a qualified provider of service per Health Plan policy

**Long QT Syndrome Full Gene Sequence Analysis**

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing for Long QT Syndrome, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Clinical signs indicating moderate to high pre-test probability of Long QT syndrome, but diagnosis cannot be made with certainty by other methods (i.e. Schwartz criteria of 2-3), or
  - Confirmation of prolonged QTc or T-wave abnormalities [\(>460\text{ms}\) (prepuberty) or \(>480\text{ms}\) (adults)] on serial 12-lead ECGs] on exercise or ambulatory ECG, or during pharmacologic provocation testing and acquired cause has been ruled out, or
  - A prolonged or borderline prolonged QT interval on ECG or Holter monitor and acquired cause has been ruled out, or
  - Profound congenital bilateral sensorineural hearing loss and prolonged QTc, OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Biologic relative(s) (1st degree) diagnosed with LQTS clinically whose genetic diagnosis is unknown, OR
- Rendering Laboratory is a qualified provider of service per Health Plan policy.
Long QT Syndrome Deletion/Duplication Analysis†

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No mutation identified with long QT full gene sequence analysis, or
  - Neither or only one mutation in KCNQ1 or KCNE1 identified in an individual with profound congenital bilateral sensorineural hearing loss and prolonged QTC, AND
- Rendering Laboratory is a qualified provider of service per Health Plan policy

† Laboratory Testing Restriction: Testing is authorized after no mutation identified with long QT full gene sequence analysis OR neither or only one mutation in KCNQ1 or KCNE1 identified.

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<tr>
<th>NCD/LCD Jurisdiction and CPT Codes</th>
<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
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References

Lynch Syndrome (Sequencing and Deletion/Duplication Analysis)

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What Is Lynch Syndrome (HNPCC)?

- Lynch syndrome, also called hereditary non-polyposis colorectal cancer (HNPCC), is the most common known hereditary cause of colon cancer, accounting for 2-5% of all colorectal cancer cases.\(^1,2\)
- HNPCC is associated with a high lifetime risk for colorectal cancer (up to 80%) and endometrial cancer (20-60%), diagnosed at an earlier than usual age.\(^3\) The risk is also increased for small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain, sebaceous adenoma, and keratoacanthoma tumors.\(^1\) The average ages of diagnosis for colorectal, endometrial, and gastric cancers are 61, 46-62, and 56 years, respectively.\(^3\) Ovarian cancer diagnoses are typically earlier, with an average age of diagnosis of 42.5 years, roughly one-third of cases being diagnosed before the age of 40.\(^3\)
- Lynch syndrome includes the variants Muir-Torre syndrome (one or more Lynch syndrome-associated cancers and sebaceous neoplasms of the skin) and Turcot syndrome (Lynch syndrome with glioblastoma).\(^3\)
- Lynch syndrome should be suspected when the personal and/or family cancer history meets the Revised Bethesda Guidelines\(^4\) or the Amsterdam II Criteria\(^5\) (see table below).
- Lynch syndrome is an autosomal dominant syndrome that is associated with a germline mutation in one of at least five genes: MLH1, MSH2, MSH6, PMS2, and EPCAM. Children of an affected individual have a 50% risk to inherit a mutation.

Test Information

- Lynch syndrome is caused by mutations in any one of at least the following five genes:\(^3,6\)
  - MLH1 accounts for 32%-50% of HNPCC-causing mutations. Sequencing identifies most mutations. An additional 5% can only be identified by deletion/duplication analysis.
Lynch Syndrome Analysis

- MSH2 accounts for about 40% of HNPCC-causing mutations. Most are found by sequencing, but 20% are detectable only by deletion/duplication analysis.
- MSH6 accounts for 7%-14% of HNPCC-causing mutations. Most will be found by sequencing, but an estimated 7% are detectable only by deletion/duplication analysis.
- PMS2 accounts for 5%-15% of HNPCC-causing mutations. Most are found by sequencing, but 20% are only detectable by deletion/duplication analysis.
- EPCAM accounts for about 1%-3% of HNPCC-causing mutations. To date, all mutations have been deletions detectable by deletion/duplication analysis (not sequencing).

- Three main approaches to Lynch syndrome genetic testing are appropriate in different clinical situations:
  - Testing those with a suspected Lynch syndrome-related cancer should begin with microsatellite instability and/or immunohistochemistry testing on tumor tissue, which is discussed separately. If these tumor tests suggest Lynch syndrome, that individual should be offered genetic testing to look for a mutation that causes Lynch syndrome. If immunohistochemistry studies are abnormal, those results may suggest which of four possible mismatch repair genes is likely to harbor a mutation. Otherwise, genetic testing often starts with the MLH1 and MSH2 genes because they account for most Lynch syndrome cases. If these tumor tests are normal but a strong family history of Lynch syndrome-associated cancers is present (e.g., Amsterdam criteria are met), genetic testing may still be warranted — or tumor testing in another family member with the most suspicious cancer history may be considered.
  - If tumor screening is not possible, direct genetic testing may be reasonable if the individual meets certain criteria (see Guidelines below). Genetic testing usually starts with sequencing and deletion/duplication analysis of the MLH1 and MSH2 genes because they account for most Lynch syndrome cases. The first person tested should be the relative most likely to have Lynch syndrome in the family.
  - When the family Lynch syndrome mutation is known, at-risk relatives should be tested for that specific mutation only. This is often called single site mutation analysis. Detection rates approach 100%.

Guidelines and Evidence

The American College of Gastroenterology (ACG, 2009), the National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer (NSGC/CGA-ICC, jointly published, 2011) and the National Comprehensive Cancer Network (NCCN, 2014), have practice guidelines that address Lynch Syndrome genetic testing. Generally, these recommendations agree:

- Test colorectal tumors by microsatellite instability and/or immunohistochemistry first when tissue is available.
- Individuals with abnormal microsatellite instability and/or immunohistochemistry results should be offered genetic testing to identify a Lynch syndrome disease-causing mutation. Results from tumor testing should guide the genetic testing cascade. When tumor testing is not possible or results are inconclusive, genetic testing for an inherited mutation is indicated if a patient with a suspected Lynch syndrome-related cancer meets one of the first three Bethesda Guidelines or the family meets the Amsterdam Criteria (see tables below). If no affected family member is available for testing, at-risk relatives can consider genetic testing if the family meets the Amsterdam Criteria.
However, only a mutation positive result can be clearly interpreted. Mutation negative results must be interpreted with caution; the chance of inconclusive results is high because the family mutation may not be detectable. Once a Lynch syndrome disease-causing mutation has been identified, at-risk relatives should be offered genetic testing for that specific mutation.

### Revised Bethesda Guidelines

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<tr>
<th>Consider HNPCC tumor screening if <strong>ANY ONE</strong> of the following are met:</th>
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<tbody>
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<td>Colorectal cancer diagnosed before age 50</td>
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<tr>
<td>Presence of synchronous or metachronous colorectal cancer, or colorectal cancer with other HNPCC-associated tumors*, regardless of age</td>
</tr>
<tr>
<td>Microsatellite unstable (MSI-H) tumor pathology before age 60 (e.g., tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern, or other reported features)</td>
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<tr>
<td>At least one first-degree relative (parent, sibling, child) with an HNPCC-related tumor*, one of whom was diagnosed before age 50</td>
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<tr>
<td>At least two first- or second-degree relatives with HNPCC-related tumors* at any age</td>
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</tbody>
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### Amsterdam II Criteria

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<tr>
<th>HNPCC is likely when <strong>ALL</strong> of the following are met:</th>
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<tbody>
<tr>
<td>There are at least three relatives with HNPCC associated tumors*</td>
</tr>
<tr>
<td>One affected relative is a first-degree relative (parent, sibling, child) of the other two</td>
</tr>
<tr>
<td>Affected relatives are in two or more successive generations</td>
</tr>
<tr>
<td>At least one HNPCC-related tumor was diagnosed before age 50</td>
</tr>
<tr>
<td>FAP has been excluded (generally on the basis of no polyposis)</td>
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<tr>
<td>Tumors should be verified by pathology</td>
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</table>

*HNPCC-associated tumors include colorectal, endometrial, small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain tumors (usually glioblastomas associated with Turcot syndrome variant), sebaceous adenomas, and keratoacanthomas (associated with Muir-Torre syndrome variant).

### Criteria

**DNA Single-site Mutation (Family Mutation) Testing**

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous testing for inherited Lynch syndrome mutations, AND
- Family History:
  - Known MLH1, MSH2, MSH6, PMS2, or EPCAM mutation in a close blood relative (1st, 2nd, or 3rd degree)
- Age- 18 years and older, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.
Gene Sequencing and/or Deletion/Duplication Analysis of MLH1, MSH2, MSH6, PMS2, or EPCAM

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - Gene requested has not been tested previously by the same methodology (i.e., sequencing or deletion/duplication analysis), AND
- Age - 18 years or older, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Personal history of colorectal cancer (or other Lynch syndrome-related tumor*), and
  - If colorectal cancer (see figure A):**
    - MSI testing of tumor tissue shows MSI-high, or
    - IHC testing of tumor tissue detects absence of MLH1, MSH2, MSH6, and/or PMS2 encoded protein products, and
    - BRAF mutation analysis and/or MLH1 hypermethylation analysis performed if indicated (according to figure A) and not consistent with sporadic CRC (sporadic CRC is likely when the tumor has MLH1 promoter hypermethylation and/or the BRAF V600E mutation.), or
  - If other LS-associated tumor:
    - Endometrial cancer diagnosed before age 50, or
    - Presence of synchronous, metachronous colorectal, or other Lynch syndrome-associated tumors, regardless of age, or
    - Amsterdam II criteria are met:
      - ≥ 3 close blood relatives (1st, 2nd, or 3rd degree) with Lynch syndrome-associated tumor (symptomatic member can be one of the three), and
      - One should be a first-degree relative of the other two, and
      - ≥ 2 successive generations affected, and
      - ≥ 1 diagnosed before age 50, OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - ≥ 3 close blood relatives (1st, 2nd, or 3rd degree) with Lynch syndrome-associated tumor, where Amsterdam II criteria are met:
    - One should be a first degree relative of the other two, and
    - ≥ 2 successive generations affected, and
    - ≥ 1 diagnosed before age 50, and
    - Familial adenomatous polyposis (FAP) ruled out, and
  - IHC and/or LS genetic testing results from affected family member are unavailable
- Rendering laboratory is a qualified provider of service per Health Plan policy, AND
- Testing algorithm as outlined in Figure A or Figure B must be followed for payment of claim

*Lynch syndrome-associated tumors include colorectal, endometrial, small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain/CNS tumors (usually glioblastomas associated with Turcot syndrome variant), sebaceous adenomas, and keratoacanthomas (associated with Muir-Torre syndrome variant).
**Lynch syndrome genetic testing for those with colorectal cancer is generally not indicated in the absence of abnormal MSI and/or IHC results on the colorectal tumor. MSI and/or IHC became part of the standard NCCN recommended evaluation for all people with colorectal cancer under the age of 70 (at a minimum) in May 2013. As a result, most people affected with colorectal cancer who are appropriate candidates for Lynch syndrome testing should have access to MSI and/or IHC. Lynch syndrome genetic testing without MSI and/or IHC results will only be considered necessary in extenuating circumstances and will require medical necessity review.**
Figure A 8, 11
Diagnostic Testing for Symptomatic Individuals

Lynch Syndrome/HNPCC
Immunohistochemistry (IHC) Testing and/or
Microsatellite Instability (MSI) Testing

If IHC not performed, consider IHC testing before continuing

MSI – High
Normal IHC or No Results

Abnormal IHC
MSI – High or No Results

MSI – Low or Stable
IHC Normal
No Further Testing Required

Loss of MLH1 Expression
MLH1 Sequencing and Deletion/Duplication
No Mutation Detected

Loss of MSH2 Expression
BRAF V600E
MSH2 Sequencing and Deletion/Duplication
No Mutation Detected

Loss of MSH6 Expression
If BRAF not performed or No Mutation Detected
MSH6 Sequencing and Deletion/Duplication
No Mutation Detected

Loss of PMS2 Expression
PMS2 Sequencing and Deletion/Duplication
No Mutation Detected

EPCAM

No Mutation Detected

MSH6 Sequencing and Deletion/Duplication
MLH1 Sequencing and Deletion/Duplication

MSH2 Sequencing and Deletion/Duplication
No Mutation Detected

Loss of MLH1 and PMS2 Expression
BRAF V600E or MLH1 Promoter Methylation Study

No BRAF Mutation Detected and Hypermethylation Study Negative or Not Performed
MLH1 Sequencing and Deletion/Duplication

Hypermethylation Positive with Significant Family History or Early Age of Onset.
MLH1 Sequencing and Deletion/Duplication

No Mutation Detected

MSH2 Sequencing and Deletion/Duplication

MLH1 Sequencing and Deletion/Duplication

MSH6 Sequencing and Deletion/Duplication

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Figure B
Predisposition Testing for Presymptomatic/Asymptomatic Individuals

MLH1 & MSH2 Sequencing and Deletion/Duplication

No Mutation Detected

MSH6 Sequencing and Deletion/Duplication

No Mutation Detected

PMS2 Sequencing and Deletion/Duplication
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See LCD jurisdictions that refer to MolDX.

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DUP/DELETE VARIANT
No
No
N/A

81317 PMS2 GENE
FULL SEQ ANALYSIS
No
No
N/A

81318 PMS2 KNOWN FAMILIAL VARIANTS
No
No
N/A

81319 PMS2 GENE
DUP/DELET VARIANTS
No
No
N/A

References

# Lynch Syndrome (Immunohistochemistry, Microsatellite Instability)

## Procedure(s) covered by this policy:

<table>
<thead>
<tr>
<th>Procedure(s) covered by this policy</th>
<th>Procedure Code(s)</th>
<th>Requires:</th>
<th>Lab Procedure Restrictions†</th>
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† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

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## What Is Lynch Syndrome Tumor Screening?

- Lynch syndrome, also called hereditary non-polyposis colorectal cancer (HNPCC), is the most common known hereditary cause of colon cancer, accounting for 2-5% of all colorectal cancer cases.1,2
- Lynch syndrome is associated with a high lifetime risk for colorectal cancer (up to 80%) and endometrial cancer (20-60%), diagnosed at an earlier than usual age.3 The risk for several other cancers is also increased.3
- Lynch syndrome is caused by mutations in the following mismatch repair genes: MLH1 and MSH2 (together account for 90% of HNPCC mutations), MSH6 (up to 10%), and PMS2 (<5%). An additional gene called EPCAM (or TACSTD1), was found to account for 1-3% of Lynch syndrome cases.3
- Lynch syndrome gene mutations are inherited in an autosomal dominant manner, but family history alone is unreliable for identifying Lynch syndrome cases.1 Lynch syndrome mutations inherited in an autosomal recessive manner cause Constitutional MMR-Deficiency syndrome (CMMR-D).
- Individuals with colorectal or endometrial cancer due to Lynch syndrome often have abnormal immunohistochemistry (IHC) and/or microsatellite instability (MSI) results on their tumors. These tests have good sensitivity and can identify individuals at sufficient risk for Lynch syndrome to warrant follow-up genetic testing.1
- Most often, tumor screening is offered to those with cancer and a family history that suggests Lynch syndrome (see guidelines below).1,4,5
- Identifying at-risk individuals is necessary for appropriate surveillance and risk reduction.1

## Test Information

- Both immunohistochemistry and microsatellite instability evaluate formalin-fixed, paraffin-embedded tumor tissue for evidence of mismatch repair defects. Lynch syndrome is caused by mutations in mismatch repair genes.
Lynch Syndrome MSI/IHC

- **Immunohistochemistry (IHC)** detects the presence or absence of MLH1, MSH2, MSH6, +/- PMS2 mismatch repair proteins. Most Lynch syndrome-causing mutations result in protein truncation or absent protein expression, which leads to abnormal IHC staining. As a result, IHC will detect an estimated 83%-94% of underlying Lynch syndrome mutations in colorectal tumors. IHC has the distinct benefit of identifying the gene most likely to have a mutation. DNA testing can then be targeted to that specific gene.

- **Microsatellite Instability (MSI)** compares normal and tumor tissue to detect microsatellite (stretches of repetitive DNA) size changes. Lynch syndrome mutations often cause the size of microsatellites to be unstable. When tumor tissue shows high microsatellite instability (MSI-H), it is indirect evidence of an underlying Lynch syndrome gene mutation. Depending on the panel of MSI markers, 80-91% of MLH1 and MSH2 mutations and 55-77% of MSH6 and PMS2 mutations will be detected by MSI testing.

- No specific tumor screening strategy has been recommended, but studies suggest that both MSI and IHC are cost-effective.

- MSI and IHC together have better sensitivity for HNPCC than either test alone, and may be used simultaneously or sequentially.

**Guidelines and Evidence**

- The **National Comprehensive Cancer Network (NCCN, 2014)** has published practice guidelines that address MSI and IHC tumor screening for Lynch syndrome:
  - Routine tumor testing for Lynch syndrome is supported either for all CRC patients or CRC patients diagnosed at < 70 years and also those ≥70 years who meet the Bethesda guidelines.
  - "IHC and/or MSI screening of all colorectal and endometrial cancers (usually from surgical resection but may be performed on biopsies) regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome. This approach was recently endorsed for colorectal cancer by the Evaluation of Genomic Applications in Practice and Prevention Working Group from the CDC and shown to be cost effective."
  - "An alternative approach is to test all patients with CRC diagnosed prior to age 70 years plus patients diagnosed at older ages who meet the Bethesda guidelines. This approach gave a sensitivity of 95.1% (95% CI, 89.8-99.0%) and a specificity of 95.5% (95% CI, 94.7-96.1%). This level of sensitivity was better than that of both the revised Bethesda and Jerusalem (testing all patients diagnosed with CRC at age <70) recommendations. While this new selective strategy failed to identify 4.9% of Lynch syndrome cases, it resulted in approximately 35% fewer tumors undergoing MMR testing."
  - "Endometrial cancer <50 y is not included in the revised Bethesda guidelines; however, recent evidence suggests that these individuals should be evaluated for Lynch syndrome."

---

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- Consider Lynch syndrome tumor screening if any one of the following are met:
  - Colorectal cancer diagnosed before age 50
  - Presence of synchronous or metachronous colorectal cancer, or colorectal cancer with other Lynch syndrome-associated tumors*, regardless of age
  - Microsatellite unstable (MSI-H) tumor pathology before age 60 (e.g., tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern, or other reported features)
  - At least one first-degree relative (parent, sibling, child) with an Lynch syndrome-related tumor*, one of whom was diagnosed before age 50
  - At least two first- or second-degree relatives with Lynch syndrome-related tumors* at any age

* Lynch syndrome-associated tumors include colorectal, endometrial, small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain tumors (usually glioblastomas associated with Turcot syndrome variant), sebaceous adenomas, and keratoacanthomas (associated with Muir-Torre syndrome variant).

- An evidence-based recommendation from the Centers for Disease Control and Prevention sponsored Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP, 2009) found sufficient evidence to recommend Lynch syndrome tumor screening to all individuals with newly diagnosed colorectal cancer since morbidity and mortality can be significantly improved for the patient and at-risk relatives through management changes once Lynch syndrome is diagnosed. Although not yet standard of care, some centers have instituted screening for all newly diagnosed colorectal and endometrial cancer.

- A National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer (2011) Joint Practice Guideline makes the following recommendations:
  - "Microsatellite instability (MSI) and immunohistochemistry (IHC) tumor analyses should be performed on CRC or endometrial cancers as the first-line testing strategy for any patient being evaluated for Lynch syndrome (this includes individuals with CRC or endometrial cancer who meet Amsterdam I or II criteria or Bethesda guidelines)."
  - "MSI testing should include, at a minimum, the five markers included in the NCI panel."
  - "MSI and IHC should be performed on pretreated specimens."
  - "MSI and IHC can be technically challenging assays and should be performed in laboratories that have experience with these tests to minimize the possibility of false positive or false negative results."
  - "MSI and IHC should be performed, when possible, on an affected relative’s tumor when an unaffected patient is being evaluated for Lynch syndrome."
  - "Direct germline genetic testing (refers to both DNA sequencing and a technology that detects large rearrangements, insertions, deletions and duplications) may be considered on an affected or unaffected patient being evaluated for Lynch syndrome when MSI and IHC testing are not feasible."
This guideline also notes that "Approximately 25% of individuals with Lynch syndrome are not going to meet Amsterdam or Bethesda criteria so limiting MSI and IHC to individuals who meet these criteria only is inadequate and will miss a large number of individuals with Lynch syndrome."

Criteria

Lynch Syndrome tumor screening may be considered for individuals with Lynch syndrome-related cancer* according to the revised Bethesda criteria and guidelines from the National Comprehensive Care Network (NCCN).1, 2

- Testing may be considered for individuals who meet ANY of the following criteria:
  - Diagnosed with colorectal cancer <70 years; OR
  - Diagnosed with colorectal cancer ≥ 70 years AND meets at least one of the following:
    - Colorectal cancer diagnosed before age 50; OR
    - Presence of synchronous or metachronous colorectal cancer, or colorectal cancer with others Lynch syndrome-associated tumors*, regardless of age; OR
    - Microsatellite unstable (MSI-H) tumor pathology before age 60 (e.g., tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern, or other reported features); OR
    - Colorectal cancer diagnosed in one or more first-degree relatives with an Lynch syndrome-related tumor, with one of the cancers being diagnosed under age 50 years; OR
    - Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch syndrome-related tumors, regardless of age; OR
  - Endometrial cancer diagnosed before age 50, based on evidence published after the Bethesda guidelines.

*Lynch syndrome-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome.

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<th>NCD/LCD Jurisdiction and CPT Codes</th>
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<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MoIDX?</th>
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### References

Lynch Syndrome (BRAF Mutation Analysis, MLH1 Promoter Methylation Status)

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<th>Procedure(s) covered by this policy:</th>
<th>Procedure Code(s)</th>
<th>Requires:</th>
<th>Lab Procedure Restrictions†</th>
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<tr>
<td>BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant</td>
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<td>No</td>
<td>Yes</td>
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<td>MLH1 hypermethylation analysis</td>
<td>81288</td>
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What Are BRAF Mutation and MLH1 Promoter Methylation Testing for Lynch Syndrome Screening?

- Lynch syndrome, also called hereditary non-polyposis colorectal cancer (HNPCC), is the most common known hereditary cause of colon cancer, accounting for 2-5% of all colorectal cancer cases.1-3
  - Lynch Syndrome is associated with a high lifetime risk for colorectal cancer (up to 80%) and endometrial cancer (20-60%), diagnosed at an earlier than usual age.1,4 The risk is also increased for small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain, sebaceous adenoma, and keratoacanthoma tumors.1 Lynch syndrome is an autosomal dominant syndrome that is associated with a germline mutation in one of at least five genes: MLH1, MSH2, MSH6, PMS2, and EPCAM. Children of an affected individual have a 50% risk to inherit a mutation.

- People suspected to have colorectal or endometrial cancer caused by Lynch syndrome generally have tumor screening studies first.1,7,8 Tumors caused by Lynch syndrome often show microsatellite instability (MSI) and absent protein from one or more mismatch repair genes (MLH1, MSH2, MSH6, +/- PMS2) by immunohistochemistry (IHC).1,4
- If MSI or IHC shows signs of Lynch syndrome, the next step is usually Lynch syndrome genetic testing.
- However, another step may be useful before genetic testing when IHC indicates absent MLH1 protein. Absent MLH1 may be caused by Lynch syndrome, but is also frequently a sporadic finding in colorectal cancer. Additional testing can help determine whether MLH1-negative colorectal tumors (not endometrial or other Lynch syndrome-associated tumors) are sporadic or are associated with Lynch syndrome.
  - The most common cause of absent MLH1 protein is sporadic methylation of the MLH1 gene, which causes the gene to make no protein.3
  - This MLH1 methylation is often associated with a sporadic mutation in the BRAF gene.
    - BRAF is part of a cell signaling pathway that helps control cell growth. About 6-8% of colorectal cancer tumors have a BRAF mutation.10 A single mutation, called
V600E (previously called V599E), accounts for about 90% of these BRAF mutations.3

- When MLH1 protein is absent and a BRAF mutation is present, the colon cancer is rarely caused by Lynch syndrome (i.e., the cancer is usually sporadic).3
- When MLH1 protein is absent, the tumor is negative for a BRAF V600E mutation, and MLH1 promoter methylation is present, the cancer is still generally sporadic. However, other types of mutations (e.g., MLH1 epimutations that cause widespread hypermethylation or MLH1 promoter variants) may cause this result.1

- BRAF gene mutations that are inherited or occur in tumors are relevant to several other diagnoses, including:
  - Colorectal Cancer Anti-EGFR Therapy Response
  - Thyroid Cancer Prognosis
  - Noonan Syndrome

Test Information
- For Lynch syndrome-related testing, BRAF mutation analysis +/- MLH1 promoter methylation studies are done on colorectal tumor tissue.
- When BRAF is being tested because MLH1 protein was absent on colorectal tumor IHC, most laboratories test only for the BRAF V600E mutation. However, some laboratories sequence all or part of the BRAF gene (sometimes for reasons other than Lynch syndrome screening). Targeted mutation analysis is generally less expensive than gene sequencing. Because the V600E accounts for most BRAF colorectal cancer mutations, targeted mutation analysis for this one mutation is sufficient. Results of testing for this single mutation are expected to be reliable.3
- BRAF mutation analysis and MLH1 promoter methylation studies may be offered as panels or in reflex options. For instance, BRAF mutation analysis may be a reflex test when MLH1 IHC results are abnormal. MLH1 promoter methylation studies may be done as reflex test if BRAF mutation analysis is negative.

Guidelines and Evidence
The following organizations address when BRAF and/or MLH1 promoter methylation studies should be employed in evaluating the likelihood a tumor is caused by Lynch syndrome. This section does not address who should have MSI and/or IHC tumor screening for Lynch syndrome at the time of cancer diagnosis.

- The National Comprehensive Cancer Network (NCCN, 2014) includes BRAF V600E mutation and MLH1 promoter methylation status in their table that outlines "tumor testing results and additional testing strategies."1
  - For colorectal tumors that show no MLH1 protein by IHC (+/- PMS2 negative), they state "consider BRAF/methylation studies."
  - They recommend the following based on the BRAF results:

<table>
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<tr>
<th>BRAF V600E Mutation</th>
<th>MLH1 Promoter Methylation</th>
<th>HNPCC Genetic Testing?</th>
</tr>
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<tbody>
<tr>
<td>Positive</td>
<td>Not necessary</td>
<td>No</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Most likely a sporadic cancer; genetic testing only if the family history is compelling.</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Pursue MLH1 genetic testing.</td>
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</table>
• The National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer (NSGC/CGA-ICC, jointly published, 2011) guidelines state:2
  o "Both somatic hypermethylation of the MLH1 gene (an epigenetic change) and somatic mutations of the BRAF gene have been described in sporadic CRCs exhibiting MSI and/or loss of expression of MLH1. These somatic events are rarely seen in LS CRCs and therefore may be useful in determining whether a MSI-high CRC is more likely to be sporadic."
  o "MLH1 promoter methylation and BRAF V600E mutation testing may help to reduce the number of germline genetic tests needed when IHC reveals absence of MLH1 and PMS2. However, NSGC and the CGAICC did not find enough data to recommend one test over the other or both concomitantly."
  o The likelihood of identifying a germline MLH1 with both DNA sequencing and MLPA analysis is approximately 33% when MLH1 +/- PMS2 are absent on IHC and MLH1 promoter hypermethylation is not present.

• The Centers for Disease Control and Prevention sponsored Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP, 2009) published evidence-based recommendations focused on Lynch syndrome tumor screening by MSI and IHC. They include some information about BRAF mutation analysis and MLH1 promoter methylation, but do not make formal recommendations regarding these two tests.3
  o However, the CDC website provides additional information about these guidelines. For BRAF V600E mutation analysis, they find adequate evidence of clinical validity and utility with an overall recommendation of "Sufficient evidence to recommend use for the benefit of relatives."11
  o The CDC website does not address MLH1 promoter methylation, but an EGAPP supplemental evidence review (that accompanied the recommendations) states: "This supplemental evidence review did not involve a formal search or statistical summary concerning the literature on methylation testing. The literature suggests, however, that BRAF V600E mutation testing and methylation testing of the MLH1 promoter region among CRC cases with absent MLH1 protein might avoid similar numbers of sequencing tests with little loss in Lynch syndrome detection."12

Criteria

BRAF V600E Mutation Analysis or MLH1 Promoter Methylation Status

• Previous Testing:
  o IHC testing* has been performed and indicates a loss of MLH1 protein, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Personal history of colorectal cancer, and

• Rendering laboratory is a qualified provider of service per Health Plan policy, AND
### NCD/LCD Jurisdiction and CPT Codes

<table>
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<tr>
<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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**Lynch Syndrome**  
VA, NC, SC, WV  

LCD: L33779  

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<td>81288 MLH1 Promoter Hypermethylation</td>
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</table>

### References

Malignant Glioma Alkylating Agent Response (MGMT Promoter Methylation)

<table>
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<td>MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis</td>
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What Is MGMT?

- MGMT is the O6-methylguanine-DNA methyltransferase gene, which encodes an essential DNA repair enzyme. MGMT expression in tumors causes resistance to DNA-alkylating drugs. MGMT repairs the damage produced by these DNA cross linking agents.\(^1\)
- Gene methylation is a control mechanism that regulates gene expression. If the MGMT gene is hypermethylated, its expression is absent (“turned off”) or reduced (“turned down”). With less MGMT DNA repair protein present, the tumor is typically more responsive to alkylating drugs.\(^2\)
- Glioblastoma is a common and aggressive brain tumor that is often treated with alkylating drugs.\(^2\) Temozolomide is a standard systemic chemotherapy shown to be effective for malignant gliomas.\(^2\)
- About 40-50% of glioblastoma tumors exhibit MGMT hypermethylation, leading to increased chemosensitivity.\(^3,4\)
- Treatment of gliomas often includes resection, radiation, and chemotherapy. For patients over age 70, combined treatment may not be tolerated; therefore, treatment with a single agent (radiation therapy or chemotherapy) or chemotherapy with deferred radiation therapy may be considered.\(^1\)

Test Information:

- MGMT promoter methylation testing is performed on paraffin embedded tumor tissue. Quantitative methylation-sensitive PCR is used to determine MGMT gene promoter methylation levels.

Guidelines and Evidence

- The National Comprehensive Cancer Network (NCCN, 2014) has recommended that patients over age 70 with glioblastoma or gliosarcoma should have MGMT promoter methylation testing if adjuvant chemotherapy with temozolomide is being considered. Temozolomine is appropriate for those patients who are MGMT promoter methylation positive.\(^1\)

Criteria

- Testing criteria:
  - Diagnosis of glioblastoma (or gliosarcoma), and
- Good performance status (Karnofsky Performance Status, KPS, greater than or equal to 70), and
- Age 70 or greater, and
- Adjuvant temozolomide chemotherapy is being considered\(^1\), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

References

Mammostrat Breast Cancer Assay

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Description

Breast cancer is predicted to affect 229,060 individuals in the US in 2012, making it the most commonly diagnosed cancer. Additionally, it is predicted that almost 40,000 women will die of breast cancer this year. Treatment of breast cancer involves surgery, endocrine therapy for women with estrogen-receptor (ER) positive tumors, and/or adjuvant chemotherapy or radiation. Several organizations have provided decision making algorithms to assess for the risk of recurrence, and recommendations about treatment options. Most algorithms are based on the patients age, menopausal status, comorbidities, tumor size and cancer grade, axillary node involvement and ER status. Most women with breast cancer are offered adjuvant chemotherapy.

Localized staging (Stage I/II) is diagnosed in approximately 60% of patients, with a 5-year survival rate of 98%. Adjuvant chemotherapy reduces the chance for breast cancer recurrence in many, but not all, women, especially those with ER negative tumors. However, some women who receive chemotherapy do not receive a benefit of lower recurrence, but do have adverse effects from the chemotherapy. It is estimated that approximately 1 in 200 to 1 in 500 women will have a chemotoxicity-related death. Identifying the women who do not need adjuvant chemotherapy, and avoiding a potential adverse event with chemotherapy could help defray the financial and emotional cost of breast cancer treatment.

One way to learn if a woman does not need adjuvant chemotherapy is through genetic testing of the breast cancer tumor. Breast cancer assays have been developed to identify women who are at increased risk for future metastases. These assays use specific criteria to determine if adjuvant chemotherapy would be beneficial for a patient. While there are several assays on the market, this policy will address the Mammostrat assay, produced by Clarient (Aliso Viejo, CA, USA).

Currently, the challenge in treating early stage ER+ breast cancer is deciding between hormonal therapy alone or in combination with cytotoxic chemotherapy. A prognostic model to aid in the decision could help women who would not benefit from chemotherapy avoid potential harm.

According to Clarient, Mammostrat is targeted to women of all ages with early stage, ER-positive, node negative breast cancer to predict the 10 year recurrence risk, independent of proliferation or grade. To do this, Mammostrat uses five independent biomarkers that are independent of clinical predictors (i.e., grading, staging) and appeared to outperform the Nottingham prognostic index (NPI). The NPI bases its prediction on the stage, grade and number of lymph nodes involved, and predicts the risk for 15 year survival. The five biomarkers 1) play a role in cell cycle regulation, DNA replication (p53 and HTF9C), and cell differentiation (CEACAM5), 2) are expressed during cell hypoxia and stress (NDRG1), and 3) are involved in nutrient supply to cells (SLC7A5). Using Immunohistochemistry (IHC) assays, the results are
reported out as a low, moderate or high risk. Patients with a low risk result have up to a 7.6% chance that cancer will recur within 10 years without any additional adjuvant treatment, whereas a moderate risk has a 16.3% risk for recurrence and a high risk is defined as a 20.9% chance that cancer will recur within 10 years without any additional adjuvant treatment.

The scientific framework that has been proposed to evaluate genetic discoveries is “ACCE”: analytic validity, clinical validity, clinical utility and ethical, legal, and social implications. Several groups have reviewed Mammostrat for evidence of improved health outcomes in women for analytical and clinical validity found that Mammastrat had a significant association between the Mammostrat index (high vs. moderate vs. low risk) and distant metastasis 10 years. While Mammostrat has been validated across several institutions and populations, to date, all results have been performed in one laboratory. To enhance this validation, it should be demonstrated that identical results can be obtained in multiple laboratories. Clinical utility trials have not been conducted.

As a result of the above guidelines, genetic testing is not approved for Mammostrat testing until evidence of clinical utility has been proven.

**Criteria**

Genetic testing is not approved for the Mammostrat multi-gene assay on tumor tissue because it is currently considered experimental, investigational or is unproven.

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<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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<tr>
<td>Mammostrat Breast Cancer Assay</td>
<td>Oncotype DX breast cancer assay; Breast Cancer Gene Expression Ratio; MammaPrint; Rotterdam 76-Gene Signature; 41-gene signature assay; Amsterdam 70-Gene Profile</td>
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<td>Yes</td>
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**FL**


**PR, VI**

LCD: L29343 [Link](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=29343&ContrId=371&ver=5&ContrVer=1&SearchType=Advanced&bc=KAAAAAgAAAAA%3d%3d&)

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References

**MUTYH Associated Polyposis**

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**Description**

*MUTYH* Associated Polyposis (MAP) (OMIM #608456) is an autosomal recessive syndrome.¹ Individuals who are homozygous or compound heterozygous for MUTYH mutations account for 0.4% to 1.9% of all cases of colorectal cancer (CRC).²,³ MAP is characterized by the development of multiple colorectal adenomas, hyperplastic polyps, and CRC.⁴,⁵ The presentation is quite variable; ranging from classical polyposis indistinguishable from familial adenomatous polyposis (FAP) to atypical FAP with less than 10 adenomas and/or CRC.³ Most patients present with a phenotype similar to attenuated familial adenomatous polyposis (AFAP) with less than 100 polyps (approximately 15-100 polyps). Various studies have demonstrated biallelic MUTYH mutations in approximately 30% of patients with between 10 and 100 polyps and no germ-line APC mutations.⁶,⁷ However, the number of polyps can exceed 100.³ In the classical form of FAP, biallelic MUTYH mutations account for 7-22% of all APC mutation-negative cases.⁴,⁷,⁸ One study observed biallelic MUTYH mutations in 9% of patients with atypical FAP (i.e. <10 adenomas, age range from 33 to 64 years).⁹ In this study, of 33 patients with MAP the mean age of diagnosis of polyposis coli was 43 years (range 28 to 64 years).⁹ The lifetime risk for CRC in patients with MAP is between 32% and 55%, and a high penetrance of biallelic MUTYH mutations has to be assumed.⁶,¹⁰ The average age of onset of CRC in patients with MAP is between 43 and 48 years, with a range from 29-72 years.³,⁹,¹⁰ The exact risk of CRC associated with monoallelic mutation carriers remains uncertain; most large studies have described an odds ratio of <1.5.¹¹,¹² The median age of presentation is in the mid forties to late fifties.

Extracolonic features associated with MAP include upper gastrointestinal neoplasms, congenital hypertrophy of the retinal pigment epithelium (CHRPE), osteomas, and desmoid tumors.³,¹³-¹⁷ However the presence of these extracolonic features has been reported in only a small portion of patients with MAP (7% to 18%).³ Breast cancer, ovarian cancer, endometrial cancer, bladder cancer, and sebaceous carcinomas have also been reported in patients with MAP.¹⁰,¹⁶,¹⁸-²⁰ The median ages of onset of breast, ovarian, bladder and skin cancer ranged from 51 to 61 years in a study involving 276 patients with MAP.¹⁹ It has also been observed that there is a phenotypic overlap between MAP and Lynch syndrome, although additional studies are required to better define this wider phenotype and the actual incidence of these extraintestinal features.¹⁰,¹⁹
MAP is caused by biallelic mutations in the MUTYH gene. MUTYH is a DNA glycosylase responsible for the repair of oxidative DNA damage. If a mistake is not corrected by MUTYH then a transversion will occur in the genes that have undergone oxidative damage the next time the DNA is copied. These substitutions tend to accumulate in the adenomatous polyposis coli (APC) and Kirsten rat sarcoma (K-Ras) genes. Mutations in either of these genes can begin the process of tumorogenesis, which may lead to the development of adenomas and possibly carcinomas. Of note, adenocarcinomas in patients with MAP tend to demonstrate low microsatellite instability (MSI); in contrast to the adenocarcinomas in patients with Lynch syndrome which generally demonstrate high MSI. Most of the mutations found in the MUTYH gene are missense mutations (47%). The two most common missense mutations in the MUTYH gene are the Y179C (previously known as Y165C) and G396D (previously known as G382D) mutations.

It is not easy to distinguish patients with FAP (due to APC mutations) from patients with MUTYH associated polyposis given 1) the high rate of de novo mutations in the APC gene which result in a single affected individual in a family, 2) the high carrier rate of MUTYH mutations which can lead to a pseudodominant pattern of inheritance, and 3) the fact that some of the extracolonic features associated with FAP and Lynch syndrome have been reported in a small number of patients with MAP.

The National Comprehensive Cancer Network (NCCN)’s practice guidelines on colorectal cancer screening (2012) recommend genetic counseling and testing for MUTYH mutations for individuals with a personal history of multiple adenomatous polyps (>10 adenomas) and a family history that is consistent with autosomal recessive inheritance. When polyposis is present in a single individual with a negative family history, testing for a de novo APC mutation is recommended, followed by testing for MUTYH mutations if the APC mutation test is negative. According to NCCN, if there is a clear pattern of autosomal dominant inheritance, and the absence of an APC mutation, MUTYH testing is unlikely to be informative. However, the possibility of a “pseudodominant” inheritance pattern cannot be ruled out. Therefore, testing for MUTYH mutations in these situations may be reasonable.

A combination test including APC testing and screening for the two most common MUTYH mutations is available and may be a good approach for patients with adenomatous polyps. Whether done as part of the combination test or as a separate test, APC testing should always include testing for point mutations and large rearrangements to maximize mutation detection. In North Americans, MUTYH genetic testing often begins with the Y179G and G396C mutations and proceeds to full sequencing of the open reading frame and splice sites if the patient is found to be heterozygous for one of these two mutations. The concern with this approach is that it will miss those patients who carry two MUTYH mutations other than Y179C or G396D. Studies have found that 8.3 to 20% of polyposis patients with biallelic MUTYH mutations identified through full sequencing did not have either of the two common mutations. As a result, it is appropriate and cost-effective to begin testing the APC gene and if negative, testing for the two common MUTYH mutations in Caucasian polyposis patients with Northern European ancestry. However, full sequencing of the MUTYH gene is indicated if no mutations are found in APC or in the initial MUTYH two mutation screening test. Full sequencing of the MUTYH gene is also appropriate for anyone who is not Caucasian with Northern European ancestry.

Identification of the familial mutation in an affected patient is a prerequisite for predictive testing in asymptomatic persons at risk for MAP. This would include the siblings of affected individuals who should be tested for the known family mutations only. Testing may also be appropriate for asymptomatic individuals who have two or more siblings with characteristics of MAP, and a family history that is
consistent with autosomal recessive inheritance. In these situations, consider testing an affected sibling first. **Prenatal diagnosis for MUTYH is not covered.**

If a patient is biallelic MUTYH mutation negative they should be managed according to the polyposis phenotype, including classical or attenuated FAP. If a patient is biallelic MUTYH mutation positive, management is based on their presentation. This protocol includes complete colonoscopy at biannual intervals starting from 18-20 years and esophagastroduodenoscopy starting between 25-30 years. Additional screening for the extraintestinal cancers has not been recommended.\(^\text{19}\) The rationale is that these cancers occur at a relatively advanced age and the belief that more intensive surveillance measures is unlikely to be helpful.\(^\text{19}\) For patients with monoallelic MUTYH mutations, most authors recommend that they follow the general population screening guidelines. However, the authors of one study recommend that heterozygous carriers be managed in a manner similar to relatives of patients with apparently sporadic CRC.\(^\text{10}\)

**Criteria**

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

**Known MUTYH Family Mutation(s) Testing**

- **Genetic Counseling:**
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- **Previous Testing:**
  - No previous genetic testing for known MUTYH family mutation(s), AND
- **Screening for Asymptomatic Individuals:**
  - Two known MUTYH mutations in a sibling, or
  - Both parents with one or two known MUTYH mutations, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**MUTYH Targeted Mutation Analysis for Y179C and G396D Mutations**

- **Genetic Counseling**
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- **Previous Testing:**
  - No previous MUTYH testing, AND
- **Diagnostic Testing for Symptomatic Individuals:**
  - \(\geq 10\) cumulative adenomatous or hyperplastic colonic polyps, and
  - No mutation detected on APC screening, or
  - Recessive pattern of inheritance (e.g. family history positive for only an affected sibling), OR
- **Predisposition Testing for Presymptomatic/Asymptomatic Individuals:**
  - One or more full siblings with \(\geq 10\) adenomatous colonic polyps, OR
- Rendering laboratory is a qualified provider of service per Health Plan policy.
Full Gene Sequencing of MUTYH Gene†

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - Heterozygous for Y179D or G396D mutation, or
  - Negative for MUTYH targeted mutation analysis (Y179C and G396D), and
  - No previous MUTYH full sequencing, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Non-Caucasian/Non-Northern European ancestry, and
  - ≥10 cumulative adenomatous or hyperplastic colonic polyps, and
  - No mutation detected on APC screening, or
  - Recessive pattern of inheritance (e.g. family history positive for only an affected sibling), OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Non-Caucasian/Non-Northern European ancestry, and
  - One or more full siblings with ≥10 adenomatous colonic polyps, OR
- Rendering laboratory is a qualified provider of service per Health Plan policy.

†Lab Testing Restrictions: Heterozygous for Y179D or G396D mutation, or negative for MUTYH targeted mutation analysis (Y179C and G396D).

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<th>Required ICD9 Codes?</th>
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See LCD jurisdictions that refer to MolDX.


81401 MOPATH PROCEDURE LEVEL 2 | MUTYH (mutY homolog [E.coli]) | No | No | N/A |
References

27. NCCN. Clinical practice guidelines in oncology: colorectal screening.; National Comprehensive Cancer Network; 2012 v.2,


Niemann Pick Disease, Types A and B

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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specific sequence to be followed or additional information is required and must be supplied by the lab performing procedure(s) for full

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Description

Acid Sphingomyelinase (ASM) deficiency is a lysosomal storage condition that is made up of previously known Niemann Pick type A and Niemann Pick type B. NPA is associated with more severe manifestations while NPB is later onset and a less severe course. Both conditions are the result of mutations in a single gene, SMPD1, and can be classified as neuronopathic with death in early childhood (Niemann Pick A – NPA) or non-neuronopathic (Niemann Pick B – NPB). ASM, as a whole, is characterized by hepatosplenomegaly and deterioration of lung function, with symptoms. Individuals with NPA also show developmental delay with a loss of milestones and cherry-red spots in the macula of the retinal. Symptoms of NPA can generally be seen starting at 3 months of age, with neurological deterioration beginning by one year of age and death usually occurring by age 3.1 Individuals with NPB typically develop symptoms later than early infancy and usually have a hematological disorder, such as anemia or thrombocytopenia. NPB is associated with short stature and low weight gain2, and while affected individuals can have neurological findings, they tend to be mild or non-progressive.1,3 Individuals with NPB can live into adulthood. There have been documented cases of pregnancies in mildly affected women.

ASM is seen in all populations, with NPA typically seen in Ashkenazi Jewish descent and NPB typically being pan-ethnic.4 The prevalence of ASM is estimated to be 1 in 250,000, with over 100 mutations described causing ASM.4,5 There is a founder effect, with certain alleles seen more frequently in specific populations, including individuals of Ashkenazi Jewish and North African descent. Three common mutations in the Ashkenazi Jewish population are associated with a more severe NPA phenotype,4,6 and are seen in approximately 1 in 70 - 1 in 90 individuals.3,6 Individuals in other populations that have been diagnosed with NPA have unique alleles.4 In contrast, one common mutation has been identified that is associated with NPB. This mutation accounts for ~90% of disease causing alleles from the Maghreb region of North Africa (i.e., Tunisia, Algeria, and Morocco), 100% of disease causing alleles in Grand Canaria Island,7 and approximately 20%-30% of disease causing alleles in persons of North African descent in the United States that cause NPB.

Genotype-phenotype correlation has been observed for one common mutation to cause a milder NPB disease course.9 Other alleles seen in various populations have been associated with severe, intermediate or mild disease.4,9
ASM is inherited in an autosomal recessive inheritance pattern. Because ASM is recessive, individuals usually do not have other affected family members. Parents of an affected individual are obligate carriers, while siblings have a 50% chance of being carriers of the condition, a 25% chance of not being a carrier, and a 25% chance of being affected. Carriers of ASM are asymptomatic and do not exhibit any features of the condition.

Preventive use of genetic testing on a population wide basis, for any condition, may be cost-effective if genotypic information can be shown to predict disease risk. Population-wide screening is ethically justifiable only if there is an efficacious and cost-effective intervention to prevent the disorder in those who are identified as being at increased risk. Therefore, population wide carrier screening for ASM is not recommended unless an individual is of Ashkenazi Jewish descent.6

A diagnosis of ASM most often occurs through biochemical testing for acid sphingomyelinase deficiency. Diagnostic testing requires measurement of acid sphingomyelinase enzyme activity in peripheral blood lymphocytes or cultured skin fibroblasts, molecular genetic testing through targeted mutation analysis for the common founder mutations, sequence analysis of the SMPD1 gene, or deletion/duplication testing. Individuals with ASM tend to exhibit less than 10% of enzyme activity as compared to unaffected individuals. Targeted mutation analysis is appropriate for individuals within at-risk populations and will detect between 20%-100% of disease causing mutations. In contrast, sequence analysis can identify ~95% of mutations in individuals with a positive biochemical analysis. Deletion/duplication analysis is available clinically for individuals who test negative on sequence analysis. However, to date, there have not been any identified deletions or duplications reported that cause ASM.10

Once a deleterious mutation has been identified, relatives of affected individuals can be tested. Carrier testing is not available through biochemical assay, as there is overlap of enzyme activity between carriers and non-carriers. Individuals identified as carriers for ASM can have prenatal testing of their fetus. Prenatal testing is available and is can be performed through mutation analysis if both parental mutations are known,10 or biochemical assay if both mutations are not known.

Carrier screening for certain genetic conditions can occur based on an individual’s ethnic background. One of these backgrounds with a higher risk for disease is the Ashkenazi Jewish population. This population is at a higher risk for carrying several autosomal recessive conditions including: Tay Sachs Disease, Gaucher Disease, Canavan Disease, Familial Dysautonomia, Niemann-Pick Type A, Bloom Syndrome, Fanconi Anemia and mucolipidosis IV. Cystic Fibrosis is not seen more frequently in the Ashkenazi Jewish population, however, three common mutations are the cause of the majority of CF cases, and therefore there is a higher detection rate in this population. See Ashkenazi Jewish testing policy for more information.

The American College of Medical Genetics (ACMG) supports offering carrier testing for ASM to individuals of Ashkenazi Jewish descent of testing for the common mutation. It is anticipated that the detection rate will be ~90%. This test should be offered to individuals of reproductive age, preferentially prior to pregnancy, with genetic counseling performed by a genetic counselor. Counseling should include the following: 1) a description of the condition, 2) discussion of carrier risk associated with a negative test result, 3) the risk of passing the gene onto future offspring, and 4) discussion of the implications of a positive test on other family members. For ASM, a discussion that carrier testing may identify someone who carries two disease causing alleles, but is asymptomatic. ACMG supports the testing of individuals of AJ descent, even when
their partner is non-Ashkenazi Jewish. In this situation, testing would start with the individual who is Jewish and reflex back to the partner if necessary.6

The American College of Obstetrics and Gynecologists (ACOG) recommends individuals of who are considering a pregnancy or are pregnant should consider testing if at least one member of the couple is Ashkenazi Jewish or has a relative with ASM. If the woman is pregnant, testing may need to be conducted on both partners simultaneously in order to receive results in a timely fashion. If one or both partners are found to be carriers of ASM, genetic counseling should be provided, and prenatal testing offered, if appropriate. Finally, relatives of any individual found to be a carrier should be contacted and told of the carrier status so that they may make informed reproductive decisions.11

As a result of the above guidelines, genetic testing should be approved to confirm a diagnosis in anyone who meets clinical criteria for ASM. Individuals who have a family member with a known ASM mutation(s) should be tested for that/those mutation(s). Individuals who meet clinical and/or biochemical criteria for ASM should be offered sequence analysis. Individuals from specific ethnic groups can be offered targeted mutation analysis, including individuals of Ashkenazi Jewish background with a severe neurodegenerative form of the disease suggestive of NPD-A and individuals of North African descent with NPD-B, targeted mutation analysis is the molecular genetic testing method of choice. If targeted mutation analysis does not identify both mutations in individuals with enzymatically confirmed ASM deficiency, sequence analysis of SMPD1 should be considered.10 If they test negative, and do not meet any other criteria for genetic testing (i.e., are not symptomatic), they should not continue on to sequence analysis. Deletion and duplication analysis is thought to have a very low return in finding mutations, and therefore is not recommended as a form of testing.10

Healthcare management after diagnosis includes treatment for current manifestations, as well as prevention for secondary complications. This can vary depending on whether NPA or NPB is being treated. Physical therapy for neurological issues, as well as treatment for feeding and sleeping difficulties can help the quality of life for both the NPA patient and their family. Treatment of thrombocytopenia, pulmonary disease and elevated cholesterol is essential in prolonging the life of an individual with NPB. NPB is associated with growth failure, therefore ensuring that adequate calories are ingested is necessary. Bone marrow transplantation (BMT) and enzyme replacement therapy (ERT) have brought more permanent relief from symptoms. BMT can benefit those with NPD who do not have neurological involvement. BMT in individuals with neurological disease should be considered experimental.12 ERT trials are underway in adults with NPB, with phase one being completed, phase 1b trials being currently initiated, and phase 2 recruiting in the planning stages.13 Stem Cell replacement trials in NPB have also been performed with limited success.12

Criteria

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

Known Niemann Pick Type A or B Mutation Family Testing

- Genetic Counseling
Niemann Pick Disease, Types A and B

- Pre and post-test counseling by a medical geneticist, genetic counselor, or neurologist, AND
- Previous Testing:
  - No previous genetic testing for Niemann Pick A or B, AND
- Diagnostic and Predisposition Testing:
  - Niemann Pick A or B family mutation identified in biologic relative(s), OR
- Prenatal Testing:
  - Niemann Pick A or B mutation identified in both biologic parents, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Niemann Pick A or B Targeted Mutation Analysis

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist, genetic counselor, or neurologist, AND
- Previous Genetic Testing:
  - No previous genetic testing for Niemann Pick A or B
- Diagnostic Testing for Symptomatic Individuals:
  - Hepatosplenomegaly, and
  - Evidence of interstitial lung disease on chest radiograph, and
  - Developmental Delay, and
  - Cherry Red Maculae, and/or
  - Hyperlipidemia, and
  - Thrombocytopenia, OR
- Predisposition/Carrier Testing for Presymptomatic/Asymptomatic Individuals:
  - Biologic relative(s) (1st degree) diagnosed with Niemann Pick A or B clinically, and no family mutation identified, or
  - Ashkenazi Jewish ancestry and intention to reproduce, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Niemann Pick A or B Full Sequence Analysis

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist, genetic counselor, or neurologist, AND
- Previous Genetic Testing:
  - If Ashkenazi Jewish, common mutations have been tested and resulted negative
- Diagnostic Testing for Symptomatic Individuals:
  - Measurement of acid sphingomyelinase (ASM) enzyme activity in peripheral blood lymphocytes or cultured skin fibroblasts (in symptomatic individuals) with equivocal result where suspicion of clinical diagnosis remains high, and
  - Hepatosplenomegaly, and
  - Evidence of interstitial lung disease on chest radiograph, and
  - Developmental Delay, and
  - Cherry Red Maculae, and/or
Niemann Pick Disease, Types A and B

- Hyperlipidemia, and
- Thrombocytopenia, OR

Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
- Biologic relative(s) (1st degree) diagnosed with Niemann Pick A or B clinically, and no family mutation identified, and
- If Ashkenazi Jewish, common mutations have been tested and resulted negative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

### NCD/LCD Jurisdiction and CPT Codes

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### References

**Niemann Pick Type C**

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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specific sequence to be followed or additional information is required and must be supplied by the lab performing procedure(s) for full claim payment.

**Description**

Niemann-Pick Disease, type C (NPC) is a lipid storage condition that can present in infancy, mid-to-late childhood or adulthood, with the classic presentation in mid-to-late childhood. Symptoms fall into one of three categories: visceral, neurological and psychological. The presentation of clinical symptoms at each stage is different, with infants typically presenting with hypotonia and developmental delay, with or without lung and liver disease. Children with NPC exhibit progressive ataxia, vertical supranuclear gaze palsy (VSGP) and dementia, while adults who develop NPC usually have an onset of progressive cognitive impairment or other psychiatric symptoms. The lifespan of individuals with NPC is shortened. There is a wide variability with disease progression and survival rate, which can range from just a few days to, in rare circumstances, 60 years. Most individuals survive between 10-25 years. The most severe symptoms are seen in infants and include ascites; liver disease can result in the death of an infant in a few days to a few months.

Two genes have been associated with NPC: NPC1 and NPC2. The proteins of these genes are thought to work together in the cellular transport of cholesterol and other molecules. Most (90-95%) individuals with NPC have at least one identifiable gene mutation in NPC1. Only 30 families have been found to have mutations in the NPC2 gene, making mutations in this gene rare (about 4% of NPC cases). Historically, Niemann-Pick Type D was used to describe a subgroup of individuals from Nova Scotia, Canada. However, a mutation was found in NPC1, therefore no longer justifying a distinct category for this subgroup.

NPC is thought to have a prevalence of 1 in 120,000 livebirths. There are a few populations that have a founder effect, including French Acadians of Nova Scotia, Canada originally from Normandy France; individuals of Hispanic descent in the Upper Rio Grande valley of the United States; and a Bedouin group in Israel. There have been over 200 mutations described that cause NPC. Genotype-phenotype correlation is difficult to determine as most individuals are compound heterozygotes; however, there has been observation of some alleles being associated with mild or severe disease.

NPC is inherited in an autosomal recessive inheritance pattern. Because NPC is recessive, individuals usually do not have other affected family members. Parents of an affected individual are obligate carriers, while siblings have a 50% chance of being carriers and a 25% chance of being affected. Carriers of NPC are asymptomatic and do not exhibit any features of the condition.
Recently, an NPC suspicion index has been presented as a way to identify individuals with a strong suspicion of NPC, versus those who may need further evaluation and those whose suspicion is low.¹¹ This index comprises ranked assessments of visceral, neurological and psychiatric signs and symptoms that are specific to NPC, taking family history into account, to provide an NPC risk prediction score. Patients scoring ≥70 should be referred for immediate testing. Those scoring from 40-69 should be evaluated for further signs and symptoms of a differential diagnosis. Scores below 40 have a low suspicion of NPC.¹¹

Once a diagnosis of NPC is suspected, diagnosis could occur through multiple venues, including: biochemical testing demonstration of abnormal intracellular cholesterol homeostasis in cultured fibroblasts⁷,¹², molecular genetic testing of the \textit{NPC1} and \textit{NPC2} gene, and/or deletion/duplication testing. Biochemical testing must occur in living cells, thus necessitating the use of skin fibroblasts. Fibroblasts are cultured in an LDL-enriched medium, and then fixed and stained with a compound called ‘filipin’. To perform biochemical testing, filipin interacts with unesterified cholesterol to make specific cholesterol-filled complexes in ~80-85% of cases. When this testing indicates an individual is affected, sequence/mutation analysis should be considered. However, genetic testing may also be useful when this staining is not absolute in order to have a more definitive diagnosis. Sequence analysis can identify ~80-90% of mutations in the \textit{NPC1} gene and virtually 100% of mutations in the \textit{NPC2} gene.¹³ Deletion/duplication analysis is available clinically for individuals who test negative on sequence analysis. However to date, there have been few identified deletions or duplications in the \textit{NPC1} gene and no identified deletions or duplications reported in the \textit{NPC2} gene.¹³ As this type of testing advances, individuals may be identified, at this time the detection rate is unknown and is thought to be low.¹³

Once a deleterious mutation has been identified, relatives of affected individuals can be tested. Carrier testing is not available through biochemical assay, as there is overlap of enzyme activity between carriers and non-carriers. Because of the variability of age of onset and presenting symptoms, individuals undergoing carrier testing should be aware that they could be identified as carrying two mutant alleles, and thus affected. Individuals identified as carriers for NPC can have prenatal testing of their fetus. Prenatal testing is available and it can be performed through mutation analysis on CVS or amniocytes if both parental mutations are known.¹³ Biochemical assay can be performed if both mutations are not known, however, it is usually performed as a last resort.⁷

As a result of the above recommendations, genetic testing should be approved to confirm a diagnosis in anyone who meets biochemical or clinical criteria for NPC. Individuals who have a family member with a known NPC mutation(s) should be tested for that/those mutation(s) only. Prenatal testing should be offered to couples who have had a previous child die of NPC. Individuals who meet clinical and/or biochemical criteria for NPC should be offered sequence analysis. Because of the low yield in identifying whole or partial gene duplications or deletions in the \textit{NPC1} or \textit{NPC2} gene, deletion/duplication testing should not be approved.

Healthcare management after diagnosis includes treatment for current symptoms. This generally includes medications to prevent the onset of seizures, although treatment of liver disease, sleeping dysfunction or other symptoms should be considered as well. There is no definitive therapy available for NPC. Bone marrow transplantation (BMT), liver transplantation or the use of cholesterol lowering drugs did not prevent the progression of neurological disease.
Criteria
Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

**Known Niemann-Pick Disease Type C Mutation Family Testing**

- **Genetic Counseling**
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- **Previous Testing:**
  - Biochemical testing performed on cultured skin fibroblasts showing abnormal intracellular cholesterol homeostasis AND
  - No previous genetic testing for Niemann-Pick C
- **Diagnostic and Predisposition Testing:**
  - Niemann-Pick C family mutation identified in biologic relative(s), OR
- **Prenatal Testing:**
  - Niemann-Pick C identified in biologic relative(s), AND
- **Rendering laboratory is a qualified provider of service per the Health Plan policy.**

**Niemann-Pick C Syndrome Full Sequence Analysis of NPC1 or NPC2**

- **Genetic Counseling**
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- **Previous Genetic Testing:**
  - Biochemical testing performed on cultured skin fibroblasts showing abnormal intracellular cholesterol homeostasis, and
  - No previous genetic testing for Niemann-Pick C, AND
- **Diagnostic Testing for Symptomatic Individuals:**
  - Hepatosplenomegaly and/or liver failure, or
  - Central hypotonia or low muscle tone characterized by frequent falls and clumsiness, or
  - Ocular motor abnormalities, especially saccadic eye movements (SEM) and vertical supranuclear gaze palsy, or
  - Delayed or arrested speech development with or without cognitive impairment, or
  - Cerebellar ataxia, or
  - Seizures, or
  - Dystonia, or
  - Dysphagia, OR
- **Predisposition Testing for Presymptomatic/Asymptomatic Individuals:**
  - Biologic relative(s) (1st, 2nd, or 3rd degree) diagnosed with NPC clinically, and no family mutation identified, AND
- **Rendering laboratory is a qualified provider of service per the Health Plan policy.**
Niemann-Pick Deletion/Duplication Analysis

Rationale: Clinical utility of Deletion/Duplication testing for NPC has not been well established. Because of the low yield in identifying whole or partial gene duplications or deletions in the *NPC1* or *NPC2* gene, deletion/duplication testing should not be approved.

References

Description

Colon cancer is predicted to affect 143,460 individuals (103,170 colon and 40,290 rectal; 73,420 men and 70,040 women) in the US in 2012, making it the third most commonly diagnosed cancer.\(^1,2\) Additionally, it is predicted that almost 51,690 men and women will die of colon and rectal cancer this year.\(^1,2\) The median age of diagnosis of colon cancer is 69, with approximately 61% of cases diagnosed over the age of 65.\(^2\) Treatment of colon cancer typically involves surgery, and is curative if the cancer has not spread. Adjuvant chemotherapy and/or radiation may be needed if the cancer has spread outside the wall of the colon.

The average 1- and 5-year survival rate for colon cancer is 83% and 64%, respectively. Localized staging (Stage I/II) is diagnosed in only 39% of patients, with a 5-year survival rate of 90%.\(^1\) The low rate of diagnosis of a localized cancer is in part a result of underutilization of surveillance. When a cancer has spread into adjacent organs or lymph nodes, the survival rate decreases to approximately 69%. When it metastasized to distant organs, the 5 year survival drops to around 12%. Adjuvant chemotherapy is typically given to individuals with stage III cancer, as stage I and II can typically be treated with surgery alone. However, some individuals with stage II cancer have poor outcomes. It has been suggested that individuals with stage II cancer be offered adjuvant chemotherapy, as it can improve disease-free survival rates.\(^3\) Currently, the challenge in treating stage II colon cancer is knowing who may have a prognosis similar to a stage III diagnosis and should be treated with adjuvant chemotherapy. A prognostic model to aid in the decision could help individuals who would benefit from chemotherapy rather than surgery alone.

One way to learn if whether an individual with stage II colon cancer should consider adjuvant chemotherapy is through genetic testing of the colon cancer tumor. One colon cancer assay, Oncotype DX® Colon Cancer Assay, has been developed by Genomic Health (Redwood City, CA) to identify individuals with stage II cancer who are at increased risk for future metastases.\(^4\) This assay uses specific criteria to determine if adjuvant chemotherapy would be beneficial for a patient.

According to Genomic Health, Oncotype DX® Colon is targeted to individuals of all ages with stage II, MMR-colon cancer to predict the 3-year recurrence risk, or stage III A/B cancer to inform whether the use of oxaliplatin outweighs the risk of toxicities associated with its use.\(^4\) To do this, the Oncotype DX® Colon Cancer Assay uses a 12 gene panel to evaluate a colon cancer tumor. Seven genes are those that are associated with colon cancer, including three cell cycle genes (\(Ki-67\), \(C-MYC\), and \(MYBL2\)), three stromal genes (\(FAP\), \(BGN\), and \(INHBA\)) and \(GADD45B\). Additionally, five reference genes that normalize the expression of cancer genes are utilized. These include \(ATP5E\), \(PGK1\), \(GPX1\), \(UBB\), and \(VDAC2\). Reverse transcriptase PCR (RT-PCR) is used to analyze the mRNA expression of the 12 genes and come up with a recurrence score (RS). The RS is a continuous score between 0-100, and is meant to be used with patient’s clinical features to help inform treatment decisions. Patients with high recurrence scores are meant to have a better clinical outcome with adjuvant chemotherapy than patients with a low score. The RS is reported out as a low (<30), intermediate (30≥) or high risk (41%). Patients with a low risk result...
have up to a 12% chance that cancer will recur within 3 years without any additional adjuvant treatment, whereas an intermediate risk is defined as an 18% risk and high risk is defined as a 22% chance that cancer will recur within 3 years without any additional adjuvant treatment.4,5

The scientific framework that has been proposed to evaluate genetic discoveries is “ACCE”: analytic validity, clinical validity, clinical utility and ethical, legal, and social implications.6 Oncotype DX® Colon Cancer Assay has been reviewed by several groups and meeting presentations for evidence of improved health outcomes in individuals with colon cancer. Specifically, Oncotype DX® Colon Colon Cancer Assay has been reviewed for analytical and clinical validity. One report discussed the development of the test where the authors found that the biomarkers maintained good test performance; however, no specific analytic sensitivity or specificity calculations were provided.7 One meeting report indicated that determining MMR tumor status was important for inter-assay agreement.8 Several studies reported as meeting abstracts found the RS was a validated predictor or relapse-free progression and overall survival.9 Clinical utility was reported upon in a meeting abstract presented in 2011. It reports that the use of the RS in stage II and intact MMR colon cancer is likely to improve quality-adjusted life expectancy and be cost-saving.10 However, no other studies have been found.

As a result of the above guidelines, genetic testing is not approved for Oncotype DX® Colon Cancer Assay testing until evidence of clinical utility has been proven.

Criteria
Genetic testing is not approved for the Oncotype DX® Colon Cancer assay on tumor tissue because it is currently considered experimental, investigational or is unproven.

References
PCA3 Testing, Prostate Cancer

(Rocky Mountain Health Plan AC-5057)

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Description

The PCA3 gene is markedly unregulated in cancerous prostate cells and is not expressed, or expressed only at very low levels in normal or hyperplastic prostatic tissue. The identification of the PCA gene relies on detection of the overexpression of the associated messenger ribonucleic acid (mRNA) in blood or urine after a digital rectal examination. Most testing is done on urine.

Criteria

- Prostate cancer antigen testing (PCA3) may be indicated in males with ALL of the following:
  - Prostate specific antigen (PSA) continues to rise after a previously negative biopsy of the prostate, and
  - Invasive treatment would be considered, and
  - Testing is NOT being done as part of a program of active surveillance

References

10. European Association of Urology (EAU). Guidelines on Prostate Cancer. 2011.. The EAU guidelines on prostate cancer include the following regarding PCA3 testing (EAU, 2011; Heidenreich, et al., 2011)


Peutz-Jeghers Syndrome

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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Description

- Peutz-Jeghers syndrome (PJS) is a genetic disorder characterized by the development of polyps (hamartomas) in the stomach, small intestine and colon. About a third of affected individuals present with polyps by age 10, and by age 20, about half have clinical signs and symptoms.2
- Affected people also typically have mucocutaneous pigmented lesions — lip freckling is classic, but pigmentation may also develop in the mouth, gums, nose, perianal area, and on the fingers and toes.1,2
- In addition to gastrointestinal polyps, people with PJS have an increased risk for other cancers, including those of the pancreas, lung, breast, uterus and ovaries.2
- PJS is caused by mutations in the STK11 gene. STK11 is a tumor suppressor gene. Its normal role is to control growth and development of cells in the GI tract. Mutations in STK11 cause cells to grow and divide uncontrollably, leading to the development of polyps and an increased risk for cancer.1
- PJS is inherited in an autosomal dominant pattern. Children of an affected person have a 1 in 2 (50%) chance to be affected. New mutations are common: about half of affected people have an affected parent, while the other half have a presumably new (de novo) mutation.1
- Because of the potential early onset of polyp growth, surveillance is complex and involves monitoring at-risk individuals for related cancers, starting at with baseline colonoscopy and upper GI endoscopy before age 10.2,3
- Over 100 distinct STK11 gene mutations or deletions have been identified in people with PJS.
- Molecular genetic testing is performed in parallel by two methods for the first person tested in the family:1
  - **Sequence analysis** to identify smaller mutations in STK11. The chance of finding a mutation by sequencing is about 55% in those with a known family history, and about 70% in those with a negative family history.
  - **Deletion/duplication analysis** to identify larger deletions. The chance of finding a deletion mutation is about 45% in those with a known family history, and about 21% in those without.
  - Once a familial mutation is identified, at-risk family members can be tested using single site analysis to determine their mutation status. Please see the Peutz-Jeghers Syndrome – STK11 Family Mutation Analysis summary for more information.
- Evidence-based guidelines for the diagnosis and management of PJS were published in 2010.2 These guidelines outline clinical diagnostic criteria for PJS and surveillance recommendations, but do not specifically address the utility of genetic testing.
A clinical diagnosis of PJS may be made in an affected person when any ONE of the following is present (directly quoted):

- Two or more histologically confirmed PJ polyps
- Any number of PJ polyps detected in one individual who has a family history of PJS in close relative(s)
- Characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in close relative(s)
- Any number of PJ polyps in an individual who also has characteristic mucocutaneous pigmentation

"No clear genotype-phenotype correlation has been demonstrated in PJS, and no clear differences found between cases with STK11 mutation and in those in whom no mutation has been detected."

- The National Comprehensive Cancer Network (2012) guidelines outline similar clinical diagnostic criteria and provide some guidance on surveillance, but do not address the use of genetic testing.
  - "A clinical diagnosis of PJS can be made when an individual has two or more of the following features:
    - Two or more Peutz-Jeghers-type hamartomatous polyps of the small intestine
    - Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
    - Family history of PJS"
  - "The majority of cases occur due to mutations in the STK11 (LKB1) gene and clinical genetic testing is available."
  - Screening procedures and intervals are outlined for breast, colon, stomach, pancreatic, small intestine, cervical, ovarian, uterine, and testicular cancers.

- Clinical diagnostic criteria have been validated by genetic testing in one series of 71 patients. Of 56 patients who met clinical criteria for PJS, 94% had an STK11 mutation found by a combination of sequencing and deletion/duplication analysis. Twelve patients had only a "presumptive diagnosis" of PJS based on the presence of hyperpigmentation or isolated PJS polyps, with no known family history. No STK11 mutations were found in those 12 patients.

- The American Society of Clinical Oncologists (ASCO) position statement on genetic testing (originally published 1996; revised/affirmed in 2003 and 2010) outlines general recommendations for genetic testing for hereditary cancer syndromes and specifically addresses issues around genetic testing in at-risk children:
  - "Indications for Genetic Testing: ASCO recommends that genetic testing be offered when 1) the individual has personal or family history features suggestive of a genetic cancer susceptibility condition, 2) the test can be adequately interpreted, and 3) the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer."
  - "Special Issues in Testing Children for Cancer Susceptibility: ASCO recommends that the decision to offer testing to potentially affected children should take into account the availability of evidence-based risk-reduction strategies and the probability of developing a malignancy during childhood. Where risk-reduction strategies are available or cancer predominantly develops in childhood, ASCO believes that the scope of parental authority encompasses the right to decide for or against testing."
"Tests for high-penetrance mutations in appropriate populations have clinical utility, meaning that they inform clinical decision making and facilitate the prevention or amelioration of adverse health outcomes."

Criteria

STK11 (LKB1) gene testing may be considered for individuals with a suspected or known clinical diagnosis of Peutz-Jeghers syndrome, or a known family history of a STK11 (LKB1) mutation.

Testing is indicated for individuals whose medical and/or family history is consistent with ANY of these:

- A relative with a known deleterious STK11 (LKB1) gene mutation; OR
- A clinical diagnosis of PJS based on at least two of the following features:
  - At least two PJS-type hamartomatous polyps of the small intestine
  - Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
  - A family history of PJS

References

Prader-Willi Syndrome

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Click here for applicable Medicare NCD/LCD information

Description

Prader-Willi syndrome (PWS) is a microdeletion syndrome characterized by an insatiable appetite, developmental delay and hypotonia in childhood throughout adulthood. Other common features include hypogonadism, characteristic facial appearance and obese body habitus, as well as common behaviors including temper tantrums and compulsive traits. At birth, individuals with PWS have low birth weight, hypotonia, poor suck, and poor weight gain. Typically, by age 2, hyperphagia (insatiable appetite) with an inability to satiate sets in, and if left unchecked causes obesity. Individuals with PWS have growth hormone deficiency causing shortened stature if not treated. The major cause of morbidity and mortality is morbid obesity.

Diagnostic criteria were first proposed in 1981. In 1993, a group of clinicians with experience with PWS syndrome created the clinical criteria for diagnosis of PWS. The criteria were tested by five other clinicians, and minor alterations were made by international and national experts at several meetings. Criteria are divided into major and minor criteria, and scored. Major criteria equal 1 point and minor criteria are ½ point. Supportive findings are not scored, but help serve to increase the confidence of the diagnosis. Most of the major criteria apply to individuals of all ages, where most of the minor criteria pertain to older children and adults. Children ≤3 years require 5 points for a diagnosis, with four points coming from major criteria. Individuals ≥4 years require 8 points with major criteria comprising at least 5 points. Major criteria include: neonatal hypotonia, feeding problems in infancy, obesity, characteristic facial features, hypogonadism, developmental delay and mental retardation, food-related behavior problems, and a chromosome 15 deletion. Minor criteria include: history of decreased fetal movement and weak cry, sleep disturbances, short stature, hypopigmentation, small hands and feet, narrow hands, eye abnormalities, thick, viscous saliva, speech defects, and skin picking. These guidelines were updated in 2001 to simplify the diagnosis. The diagnosis is based on age related features of PWS.
As a result of the above guidelines, genetic testing should be approved to confirm a diagnosis or carrier status in anyone who meets clinical criteria for PWS. Genetic testing should start with DNA methylation analysis which can help point the direction of further testing. Once the diagnosis of PWS is established by DNA methylation analysis, further step wise testing consists form of FISH or CMA for the 15q11.2-q13 PWS microdeletion, testing for maternal uniparental disomy (UPD) and imprinting center (IC) defects. Additionally, genetic testing should be approved to determine the carrier status in an at risk relative with a known familial IC defect.

One gene region, 15q11.2-q13, which contains the gene SNRPN - is associated with Prader-Willi syndrome. Several alterations can disrupt the normal gene expression of this chromosomal region. This includes deletions, maternal uniparental disomy (the inheritance of two maternal 15 chromosomes), imprinting defects, and can arise from either spontaneous microdeletions or a deletion from an inherited chromosomal translocation. Paternal microdeletions are the cause of 65-75% of PWS cases.\(^2\) Deletions can be classified according to size, with larger deletions being called type 1 and smaller deletions as type 2. Parental translocations and insertions can result in a deletion of the PWS region, but are not a significant cause of PWS. Maternal uniparental disomy results in an additional 20-30% of PWS cases.\(^2\) Approximately 1-3% of cases have an imprinting defect within the imprinting center (IC) where the imprint inherited from the maternal chromosome is unable to be reset.\(^2\) Of these, 15% have a small deletion. Half are familial mutations.\(^4\) Individuals inheriting the IC defect from their mother are asymptomatic, whereas those inheriting the defect from their father have PWS. More than 60 mutations have been found in this gene.

There have been limited genotype-phenotype correlations; however, chromosomal microarray (CMA) is being used more frequently and may help identify more correlations in the future.\(^2\) Some differences between the two largest classes (microdeletion chromosome 15 and UPD) have been seen. Typically, individuals with UPD are less likely to have hypopigmentation, typical characteristic facial features or skill with jigsaw puzzles.\(^2\) They are also more likely to have a higher verbal IQ and milder behavior problems. Individuals with a microdeletion of chromosome 15 are less likely to have autism spectrum disorder or psychosis than those with UPD.\(^2\) Individuals with type 1 deletions are reported to have more compulsions and poorer adaptive behavior, intellectual ability and academic achievement than those with type 2 deletions.\(^2\)

PWS is seen in approximately 1 in 15,000 to 1 in 30,000 individuals.\(^1,2\) The risk to siblings depends on the cause of PWS. The risk to sibs can be <1% in the case of microdeletions, most cases of maternal UPD, and imprinting defects without a deletion in the imprinting center (IC). The risk could be as high as 50% in cases of chromosome translocations or insertions or imprinting defects. Lastly, the risk could be as high as 100% should a mother have a 15:15 Robertsonian translocation which is rare.

Diagnosis of PWS occurs in a stepwise fashion. To confirm a diagnosis of PWS in an individual, DNA methylation analysis should first be performed. An abnormal methylation analysis will identify all three of the principal causes of PWS, and differentiate between Angelman Syndrome and PWS. Methylation studies correctly diagnose PWS in >99% of individuals.\(^5,6\) If the methylation analysis is abnormal, a chromosome analysis with FISH targeting the 15q11.2-q13 PWS region can identify microdeletions. Chromosome analysis is needed for probands who have a microdeletion, to determine if the cause is the result of an underlying rare chromosomal rearrangement involving the proximal 15. If a microdeletion is not found, step-wise testing should look for maternal UPD and then mutations or deletions in the imprinting center (IC). Sometimes, a chromosomal microarray (CMA) has been performed previously, identifying a
microdeletion. In this case, a chromosome analysis should be performed to confirm that the proband does not have a chromosomal rearrangement causing the diagnosis.

If an imprinting defect (ID) has been found to cause PWS, 15% of those with an ID have a microdeletion in the imprinting center (IC). About half of these individuals have a familial IC, with a recurrence risk of 50%. Therefore, fathers of children with an IC deletion should have DNA methylation and dosage analysis in the PWS genetic region to determine if they carry the IC deletion. The majority of those with an imprinting defect have a \textit{de novo} epigenetic mutation and the recurrence risk to sibs is less than 1%. No parental testing would be necessary in this case.

In regard to prenatal testing, parents who have had one child with PWS caused either by deletion or UPD, and who do not have a chromosomal rearrangement, have a low recurrence risk, but could be offered prenatal testing for reassurance. Parents who have had one child with PWS caused by an IC deletion, and in whom the father is a known carrier, should be offered prenatal testing because of the high recurrence risk; DNA methylation analysis can also be used in these cases. Prenatal testing for an inherited translocation involving chromosome 15 and resulting in a deletion is relevant because of the theoretical 50% risk of PWS in the offspring.

\section*{Criteria}
Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

\subsection*{Methylation Analysis for Prader-Willi Syndrome, Molecular Analysis}

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist or genetic counselor, \textbf{AND}
- Previous Testing:
  - No previous methylation analysis, \textbf{AND}
- Diagnostic Testing for Symptomatic Individuals:
  - Neonatal hypotonia, \textbf{and}
  - Feeding problems in infancy (i.e., poor suck), \textbf{and}
  - Obesity, \textbf{and}
  - Characteristic facial features, \textbf{and}
  - Hypogonadism, \textbf{and}
  - Developmental delay or mental retardation, \textbf{and}
  - Food-related behavior problems (i.e., hyperphagia; obsession with food)

\subsection*{Chromosome and Deletion Analysis}

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist or genetic counselor, \textbf{AND}
- Previous Testing:
  - Methylation analysis results are abnormal, \textbf{and}
  - No previous chromosomal deletion analysis, \textbf{and}
Prader-Willi Syndrome

- No previous chromosome microarray sequencing, AND

**Diagnostic Testing for Symptomatic Individuals:**
- Neonatal hypotonia, and
- Feeding problems in infancy (i.e., poor suck), and
- Obesity, and
- Characteristic facial features, and
- Hypogonadism, and
- Developmental delay or mental retardation, and
- Food-related behavior problems (i.e., hyperphagia; obsession with food)

Uniparental Disomy Analysis

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist or genetic counselor, AND
- Previous Testing:
  - Methylation analysis results are abnormal, and
  - Chromosomal deletion analysis is negative, and
  - No previous UPD studies, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Neonatal hypotonia, and
  - Feeding problems in infancy (i.e., poor suck), and
  - Obesity, and
  - Characteristic facial features, and
  - Hypogonadism, and
  - Developmental delay or mental retardation, and
  - Food-related behavior problems (i.e., hyperphagia; obsession with food)

Imprinting Defect Analysis

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist or genetic counselor, AND
- Previous Testing:
  - Methylation analysis results are abnormal, and
  - Previous deletion analysis negative, and
  - Previous UPD studies negative, and
  - No previous imprinting center (IC) analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Neonatal hypotonia, and
  - Feeding problems in infancy (i.e., poor suck), and
  - Obesity, and
  - Characteristic facial features, and
  - Hypogonadism, and
  - Developmental delay or mental retardation, and
  - Food-related behavior problems (i.e., hyperphagia; obsession with food)
Family Imprinting Defect (ID) Testing

- Genetic Counseling
  - Pre and post-test counseling by a medical geneticist or genetic counselor, AND
- Previous Testing:
  - No previous ID testing, AND
- Family History:
  - Child or sibling with an imprinting center microdeletion causing PWS.

Testing is authorized for known family mutation(s) only.

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References

Prenatal Diagnosis, Chromosome Abnormalities

<table>
<thead>
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<th>Procedure Code(s)</th>
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<tr>
<td>Routine prenatal diagnosis of chromosome abnormalities (e.g., Down syndrome, trisomy 18)</td>
<td>88235, 88269, 88280, 88291</td>
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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Description

Individuals may be considered for routine prenatal testing for chromosome abnormalities (standard karyotyping) as supported by current consensus-based recommendations from the American College of Obstetricians and Gynecologists and the American College of Medical Genetics.1,2 Prenatal diagnosis may be considered via EITHER of the following methods:

- Chorionic villus sampling (CVS, performed prior to 14 weeks gestation); OR
- Amniocentesis (performed after 15 weeks gestation)

Criteria

Amniocentesis or CVS will be allowed once per pregnancy when at least one of the following criteria is met, indicating an increased risk of a chromosome abnormality in the pregnancy:

- Advancing maternal age; OR
- Abnormal first or second trimester nuchal translucency or maternal serum screening result; OR
- Previous pregnancy with a chromosome abnormality; OR
- Parental chromosome abnormality; OR
- Abnormal fetal ultrasound; OR
- Family history of known or suspected chromosome problem; OR
- Pregnancy was conceived after preimplantation genetic diagnosis (PGD); OR
- Intracytoplasmic sperm injection (ICSI) due to male-factor infertility.

References

Prenatal Maternal Serum Screening

<table>
<thead>
<tr>
<th>Procedure(s) covered by this policy:</th>
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<th>Lab Procedure Restrictions†</th>
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<td>Routine prenatal maternal serum</td>
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<tr>
<td>screening for chromosome abnormalities and birth defects</td>
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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Description

Individuals may be considered for routine prenatal screening for chromosome abnormalities (e.g., Down syndrome, trisomy 18) and birth defects (e.g., spina bifida) as supported by current evidence-based guidelines from the American College of Obstetricians and Gynecologists and the American College of Medical Genetics.¹²

Criteria

Testing by ONE of the following methods is covered one time per pregnancy:

- First trimester screening – total or free beta-HCG and PAPP-A levels performed on a maternal serum sample performed in conjunction with an ultrasound measurement of fetal nuchal translucency (NT)*
- Second trimester screening – human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), unconjugated estriol (uE3), and dimeric inhibin-A (DIA) performed on a maternal serum sample
- Integrated, step-wise sequential, or contingent sequential screening – combines results of first and second trimester screening in various testing algorithms.

*Limits on prenatal ultrasonography will depend on the insurer’s ultrasound coverage policy and are outside the scope of this program.

References

Prolaris

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<th>Procedure covered by this policy:</th>
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<tr>
<td>Prolaris®</td>
<td>84999</td>
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**Description**

About 1/3 of prostate cancer patients who have a prostatectomy, will have a "biochemical" recurrence as indicated by an elevated prostate specific antigen (PSA). Prolaris is a cell cycle progression assay marketed by Myriad Genetics.

This test identifies patients at low risk of disease recurrence with 95% certainty giving these patients confidence that additional aggressive treatment with the accompanying toxicity and adverse events is likely unwarranted. Conversely, men with high PROLARIS scores would be considered for more intensive screening and adjuvant therapy to address their more aggressive disease.

The company is performing additional clinical validation studies to expand the utility of PROLARIS. In one such recently completed study of 365 prostate cancer patients, 98.5% of prostate cancer patients with a low (favorable) PROLARIS score survived their disease after 10 years, compared to 57.6% of the patients receiving a high (unfavorable) score who died of prostate cancer within 10 years.

**Criteria**

There is a lack of peer-reviewed published evidence to support the clinical use of PROLARIS ($3400) in guiding treatment decisions in prostate cancer patients who have undergone prostatectomy. PROLARIS should be considered investigational and/or experimental pending further research.

**References**

RET/PTC Rearrangement, Thyroid Cancer

<table>
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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Description

There are three types of thyroid cancers: differentiated (including, papillary, follicular, and Hurthle cell cancer), medullary, and anaplastic (aggressive undifferentiated tumor).1,2 Papillary thyroid cancer (PTC) is the most common, accounting for 85-90% of all thyroid cancers.1,2 Rearrangements in the RET gene, leading to the formation of a certain fusion gene, are found in about 35% of PTC cases.3

Cytologic examination after a fine needle aspiration (FNA) biopsy is typically the procedure of choice and the first step of evaluation of thyroid tumors.1 About 15-20% of FNA biopsies yield indeterminate results. In cases of indeterminate results, detection of the RET/PTC rearrangements can help refine the diagnosis of PTC.3

Criteria

Testing for RET/PTC gene rearrangements is indicated in individuals with thyroid cancer who have indeterminate results from cytological examination of an FNA biopsy.

References

Rett Syndrome

**Procedure(s) covered by this policy:**

<table>
<thead>
<tr>
<th>Procedure Code(s)</th>
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<tr>
<td>Prior-authorization</td>
<td>Lab Procedure Restrictions</td>
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<tr>
<td>Known MECP2 Family mutation(s) testing</td>
<td>81303</td>
</tr>
<tr>
<td>MECP2 full sequence analysis</td>
<td>81302</td>
</tr>
<tr>
<td>MECP2 deletion/duplication analysis</td>
<td>81304</td>
</tr>
</tbody>
</table>

* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specific sequence to be followed or additional information is required and must be supplied by the lab performing procedure(s) for full claim payment.

**Description**

Over 95% of individuals who meet the clinical criteria for classic Rett syndrome have a mutation in MECP2, the gene encoding methyl-CpG-binding protein 2 (MeCP2) (24), which functions as a transcriptional modulator (15, 19, 21). MECP2 is a widely expressed nuclear protein and is especially abundant in the central nervous system. MeCP2 is considered to act as a DNA methylation-dependent transcriptional repressor, but it may have additional roles in regulating gene expression and chromatin structure (6). Rett syndrome is an X-linked dominant neurodevelopmental disorder, typically resulting from a de novo loss of function mutation in MECP2, which is estimated to affect approximately 1 in 10,000 live female births (12, 18). By age 15 years, the prevalence in females is estimated to be 1:8500 (9). It is thought to be the second most common genetic cause of mental retardation in girls (3). Over 500 mutations are listed in HGMD as causative of classic Rett syndrome and include missense/ nonsense, splicing, small indels, small deletions, small insertions, large deletions, large insertions/duplications, and complex rearrangements (22). More than 70% of the disease-causing MECP2 mutations are eight recurrent C to T transitions, which almost exclusively arise on the paternally derived X chromosome. About 10% of individuals with Rett have a C-terminal frameshift deletion in MECP2 (18).

Rett syndrome resulting from a MECP2 mutation is inherited in an X-linked manner. Most females with Rett syndrome are simplex cases (~99%) (4), as it is typically the result of a de novo MECP2 mutation. A few familial cases have been reported; these are the result of either skewed X-chromosome inactivation in unaffected (or minimally affected) female carriers (i.e., non-random X-inactivation has led to expression primarily of the normal copy of MECP2 in the mother) or germline mosaicism in an unaffected parent (male or female) with a MECP2 mutation (8). Since most occurrences of Rett syndrome are the result of a de novo mutation, risks to other family members are considered to be low. When the mother is a known carrier, the risk to her offspring of inheriting the MECP2 mutation is 50%. In addition, since germline mosaicism occurs, and “can neither be predicted nor detected” (1), prenatal diagnosis should be available to all couples who have had a child with Rett syndrome regardless of whether the disease-causing mutation has been detected in a parent (1, 4, 11).

For females with Rett, the severity of symptoms and progression of the disease can vary; these differences can be attributed to differences in the MECP2 mutation and/or to the proportion of active X-chromosomes.
with the MECP2 mutation resulting from random X-chromosome inactivation (14). Classic Rett syndrome is characterized by a period of normal development during the first 6-18 months of life followed by gradual deceleration of head growth (acquired microcephaly), replacement of purposeful hand movements with stereotypic hand wringing, loss of speech, social withdrawal and other autistic features (10). Epilepsy is common, occurring at a median age of 3 years in 72% of 97 patients described by Nissenkorn et al. (2010) (13). A recent study of Australian females with Rett syndrome notes that the median age of death was 13 years 4.8 months (5). An increased incidence of life-threatening arrhythmias associated with a prolonged QT interval is found in women with Rett syndrome (4). Because of the possibility of favorable X-chromosome inactivation (resulting in inactivation of the X-chromosome with the MECP2 mutation), a female with a MECP2 mutation may have no or minimal findings and only be identified during family studies after the birth of an affected child.

MECP2 mutations in males were thought to be lethal although approximately 60 cases have been reported. A broad range of phenotypes in males with MECP2 mutations ranging from neonatal encephalopathy to nonsyndromic mental retardation occurs (17). The most common phenotype in 46,XY males with MECP2 mutations, is a severe neonatal encephalopathy with microcephaly resulting in death before age two years. An additional phenotype with X-linked intellectual disability has been associated with MECP2 mutations as well. Affected individuals have intellectual disability ranging from mild, non-progressive in females, to severe disability in males associated with manic depression, pyramidal signs, parkinsonian features, and macro-orchidism (called the PPM-X syndrome). Affected males usually have severe intellectual disability, a resting tremor, and ataxia but do not have seizures or microcephaly. Males with 47,XXY karyotypes and some with somatic mosaicism have been reported with findings that meet clinical diagnostic criteria for classic Rett (4).

Originally described by Andreas Rett in 1966, and further delineated by Hagberg et al. in 1983, diagnostic consensus clinical criteria have been developed and modified over time. The diagnosis of Rett syndrome is considered in females in whom postnatal deceleration of head growth is observed. The most recently revised diagnostic criteria and nomenclature published by Neul et al. 2010 and validated by Percy et al. 2010 (16) are summarized and quoted below (12):

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Partial or complete loss of acquired purposeful hand skills</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Partial or complete loss of acquired spoken language</td>
</tr>
<tr>
<td></td>
<td>Gait abnormalities: impaired (dyspraxic) or absence of ability</td>
</tr>
<tr>
<td></td>
<td>Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms</td>
</tr>
<tr>
<td>Supportive Criteria</td>
<td>Breathing disturbances when awake</td>
</tr>
<tr>
<td></td>
<td>Bruxism when awake</td>
</tr>
<tr>
<td></td>
<td>Impaired sleep pattern</td>
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<tr>
<td></td>
<td>Abnormal muscle tone</td>
</tr>
<tr>
<td></td>
<td>Peripheral vasomotor disturbances</td>
</tr>
<tr>
<td></td>
<td>Scoliosis/kyphosis</td>
</tr>
<tr>
<td>Exclusion Criteria</td>
<td>Growth retardation</td>
</tr>
<tr>
<td></td>
<td>Small cold hands and feet</td>
</tr>
<tr>
<td></td>
<td>Inappropriate laughing/screaming spells</td>
</tr>
<tr>
<td></td>
<td>Diminished response to pain</td>
</tr>
<tr>
<td></td>
<td>Intense eye communications- “eye pointing”</td>
</tr>
</tbody>
</table>

Diagnosis of typical (classic) Rett syndrome includes:

Brain injury, secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that caused neurological problems. Grossly abnormal psychomotor development in first 6 months of life.
• A period of regression followed by recovery or stabilization
• All main criteria and all of the exclusion criteria
• Supportive criteria not required, although often present

Diagnosis of atypical (variant) Rett syndrome
• A period of regression followed by recovery or stabilization
• At least 2 of 4 main criteria
• 5 out of 11 supportive criteria

‘Possible Rett syndrome’ is the recommended terminology for a diagnosis given to an individual under the age of 3 years in whom a MECP2 mutation has been identified who has not yet demonstrated clear evidence of regression (12).

‘Probably atypical Rett syndrome’ is the recommended terminology for an individual under 5 years of age who has had a period of regression and two or more main criteria but does not fulfill the requirements for supportive criteria (5/11) (12).

Three atypical (variant) forms of Rett syndrome are currently included in the clinical criteria:
• Preserved speech variant (Zappella Variant)
• Early Seizure Variant (Hanefeld Variant)
• Congenital Variant (Rolando Variant) (12)

MECP2 mutations are found in the majority of individuals with the Preserved speech variant (Zappella Variant), but only rarely in those with Early Seizure Variant (Hanefeld Variant) or Congenital Variant (Rolando Variant). CDKL5 mutations are found in some individuals with the Early Seizure Variant (Hanefeld Variant) (21) and FOXP1 mutations are found in individuals with the Congenital Variant (Rolando Variant)(2).

In addition to females meeting the clinical criteria for classic Rett syndrome or atypical (variant) Rett syndrome (particularly the preserved speech variant), MECP2 mutations have been identified in individuals with a variety of phenotypes including individuals with intellectual disability, autism, molecularly-unconfirmed Angelman syndrome and severe encephalopathy in males (4). Duplication of MECP2 ranging in size from 0.3 to 4 Mb results in the MECP2 duplication syndrome, a severe neurodevelopmental disorder characterized by infantile hypotonia, severe mental retardation, poor speech development, progressive spasticity, recurrent respiratory infections and seizures. MECP2 duplication syndrome is diagnosed in males and only occasionally in females. Affected females typically have an X-chromosomal abnormality that prevents inactivation of the duplicated region (20).

To help clarify findings in patients, Neul et al (2010) recommend using nomenclature that includes both the phenotype and whether or not a MECP2 mutation has been identified. For example, individuals meeting the diagnostic criteria for classic Rett syndrome, in which a MECP2 mutation is not identified are said to have classic Rett syndrome without a MECP2 mutation. Similarly, an individual with atypical Rett syndrome, or autism with a MECP2 mutation are referred to as having atypical Rett syndrome with a MECP2 mutation or autism with a MECP2 mutation respectively (12).

Because the majority of MECP2 mutations in Rett syndrome are missense/nonsense and small deletions which are detectable with sequence analysis/mutation scanning, this method should be employed first,
specifically analysis of exons 3 and 4, the location of most mutations. (Mutations in exon 2 are not known to be associated with Rett syndrome phenotype and may be lethal (7). If a mutation is not identified in an individual who meets clinical diagnostic criteria for Rett syndrome or findings are consistent with a MECP2 mutation, deletion/duplication analysis should be performed. If a deletion is not identified, sequence analysis of exon 1 is performed. Approximately 80% of individuals with classic Rett syndrome will have a MECP2 mutation identified with sequence analysis/mutation scanning and 8% will have a deletion identified with deletion/duplication analysis. Of those individuals with atypical Rett syndrome, about 40% and 3% will have mutations detected with sequence analysis/mutation scanning and deletion/duplication analysis respectively (4).

Family-specific mutation analysis should be performed on both parents of females with Rett syndrome in whom a MECP2 mutation has been identified, and on the mothers of males with a MECP2 mutation. In addition, testing of all female sibs regardless of their clinical status and male sibs who have neurologic or neurodevelopmental abnormalities is recommended (4).

The primary clinical reasons for genetic counseling and testing in a symptomatic person are to 1) establish a specific diagnosis and avoid other diagnostic testing, 2) develop a follow-up plan for periodic ECG to screen for prolonged QTc (4) and 3) permit accurate genetic counseling and testing for family members.

Criteria

Diagnostic and Carrier Testing
Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

Known MECP2 Family Mutation Testing

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing of MECP2, and
  - MECP2 mutation identified in 1st degree biologic relative, OR
- Prenatal Testing for At-Risk Pregnancies:
  - MECP2 mutation identified in a previous child of either parent.

Full Sequence Analysis of MECP2

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous MECP2 sequencing/scanning, and
  - No known MECP2 mutation in family, AND
- Diagnostic Testing for Symptomatic Individuals:
Rett Syndrome

- Meets clinical diagnostic criteria for classic Rett syndrome, atypical Rett syndrome or probable or possible Rett syndrome, and
- Genetic testing is necessary because there is uncertainty in clinical diagnosis.

Deletion/Duplication Analysis of MECP2†

- Previous testing:
  - No previous deletion/duplication analysis of MECP2, and
  - No mutations detected in full sequencing/scanning of MECP2.

†Lab Testing Restrictions: No mutations detected in full sequencing/scanning of MECP2.

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<thead>
<tr>
<th>NCD/LCD Jurisdiction and CPT Codes</th>
<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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</tbody>
</table>

See LCD jurisdictions that refer to MolDX.


| 81302 MECP2 GENE FULL SEQ | No | No | N/A |
References

25. HUGO Gene Nomenclature Committee (HGNC) http://www.genenames.org/
Spinal Muscular Atrophy

<table>
<thead>
<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Procedure Code(s)</th>
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Description

Spinal muscular atrophy (SMA) is a group of inherited disorders that cause loss of motor neurons in the spinal cord and brainstem, which leads to muscle weakness and atrophy.1-2 There is considerable variability in age of onset and severity of symptoms, ranging from neonatal joint contractures and respiratory failure to adult onset muscle weakness with normal life expectancy. Although genetic testing has now shown that there is a continuum of phenotypes, various classification schemes have been used for SMA that have some utility in describing the disorder and predicting prognosis:1-4

- Prenatal onset form ("Type 0" proposed) is characterized by polyhydramnios, decreased fetal movements, breech presentation, arthrogryposis multiplex congenita, respiratory failure at birth, life span less than 6 months.
- Type I (infantile or Werdnig-Hoffmann type) is the most common form (60-70% of cases). It presents before 6 months of age with death often before age 2 due to respiratory failure. Affected children have severe, generalized weakness and do not ever sit without support.
- Type II (intermediate type) causes muscle weakness with onset after 6 months, although children often are able to sit alone and often survive early childhood. Intelligence is normal.
- Type III (juvenile, Kugelberg-Welander type) is milder. Onset ranges from infancy to youth, but affected people usually walk unassisted albeit with frequent falls or trouble with stairs. Survival is prolonged and intelligence is normal.
- Type IV (adult type) has much later onset with muscle weakness generally presenting at 20-30 years of age. People may or may not become wheelchair dependent, have normal lifespan and normal intelligence.

SMA is caused by autosomal recessive mutations in the SMN1 gene. Large gene deletions (exon 7 +/- exon 8) in both copies of the SMN1 gene cause SMA in the vast majority (95-98%) of affected individuals.1 The remaining 2-5% of individuals with SMA have a deletion in one SMN1 gene and a different kind of mutation in the other SMN1 gene (e.g. missense mutation).1 However, there are some unusual circumstances with the SMN1 gene that complicate genetic testing. About 4% of people have two copies of the SMN1 gene on the same chromosome for a total of three copies.1 There is also another gene, SMN2, that is adjacent to the SMN1 gene with only minor differences in the DNA sequence. An individual may have zero to five copies of the SMN2 gene on each chromosome.1 While SMN2 mutations do not cause
Spinal Muscular Atrophy (SMA) is a neuromuscular disorder caused by a deficiency of the survival motor neuron (SMN) protein, which is encoded by the SMN1 gene. The presence of SMN2 may modify disease severity, with an increased number of SMN2 gene copies being associated with milder disease. Specialized techniques are necessary to ensure that these extra and/or genetically similar genes do not lead to inaccurate results.

About 1 in 6000 to 1 in 10,000 people have a form of SMA. Carrier prevalence varies by ethnicity but ranges from about 1/40 to 1/90 for European descent populations.

Genetic testing is primarily used to diagnose SMA and to identify asymptomatic carriers who are at risk to have a child affected with SMA. There are several forms of genetic testing used in different circumstances:

- **Diagnostic testing** usually begins with SMN1 exon 7 deletion testing. Affected individuals most commonly have absent exon 7 by this assay (exon 7 is missing from both copies of the gene). If there is a high index of suspicion and exon 7 deletion testing doesn't reveal absence of both copies of exon 7, SMN1 gene dosage analysis may be done to determine if one gene copy is missing exon 7. If one copy of exon 7 is missing, SMN1 full gene sequencing may then be indicated to look for a point mutation in the other copy of SMN1. In those with a genetically confirmed diagnosis of SMA, SMN2 gene copy analysis is available to assist in predicting prognosis but is not standard of care.

- **Carrier testing** is most commonly performed by SMN1/SMN2 dosage analysis, which measures the number of SMN1 genes that contain exon 7. This is necessary given the possibility of more than one copy of the SMN1 gene per chromosome. Such testing does not detect any other types of mutations in the SMN1 gene that can cause SMA. Therefore, a negative result can reduce the likelihood of being an SMA carrier, but cannot eliminate it. Approximately 2% of SMA cases arise from a new mutation in the affected individual and one parent will not be found to be a carrier. It also is not possible to reliably predict the severity of disease based on genetic test results. Therefore, carrier testing is fraught with technical complexities. When there is a known SMN1 point mutation running in the family (e.g. not an exon 7 deletion), SMN1 known familial variant analysis is indicated and is highly reliable.

**Guidelines and Evidence**

**Diagnostic Testing**
- The International Standard of Care Committee for Spinal Muscular Atrophy issued a consensus statement in 2007 that indicated: "The first diagnostic test for a patient suspected to have spinal muscular atrophy should be the SMN gene deletion test." They provide a diagnostic algorithm that addresses when to use SMN1 deletion, copy count, and sequencing in the diagnostic process.

- The European Federation of Neurological Societies (EFNS, 2011) published guidelines on the molecular diagnosis of various neuromuscular disorders. Regarding SMA testing they state: "Screening for SMN1 deletions is indicated in SMA I-III to confirm the diagnosis and provide genetic counseling (Level B)."

**Carrier Screening**
- American College of Medical Genetics (ACMG, 2008) guidelines endorse pan-ethnic population-based SMA carrier screening regardless of whether there is a high-risk indication.
• However, American College of Obstetricians and Gynecologists (ACOG, 2009) guidelines recommend against population-based preconceptional/prenatal carrier testing, citing a lack of evidence that population carrier screening is cost-effective, technical issues, and the challenges of adequate patient education regarding testing. They recommend that carrier testing be offered when there is a family history of SMA or SMA-like disease. They also state that testing is reasonable for "those who request SMA carrier screening and have completed genetic counseling that included discussion of the sensitivity, specificity, and limitations."7

As a result of the above guidelines, CareCore has determined that genetic testing should be approved to confirm a diagnosis in anyone with sufficient clinical findings to suggest SMA in accordance with the International Standard of Care Committee for Spinal Muscular Atrophy consensus statement. Carrier screening should be reserved for those at increased risk to be a carrier based on family history and is not suitable for population-based screening at this time given the complexities and limitations of carrier testing, in addition to the lack of widespread access to testing and adequate pre-test genetic counseling.

Criteria
Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

**SMN1 Exon 7 Deletion**

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing of the SMN1 gene, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Child with hypotonia and weakness (generally symmetrical, proximal more than distal), or
  - Young adult (through twenties) onset of weakness more severely affecting the legs than arms (may be associated with frequent falls, difficulty with stairs), and
  - No obvious signs of different neurological disorder, OR
- Carrier Screening:
  - SMN1 exon 7 deletion testing is not suitable for carrier screening. SMN1/SMN2 dosage analysis (section 1-B) is necessary, OR
- Embryos or At-Risk Fetuses:
  - Both parents are carriers of an SMA mutation (at least one of which is an exon 7 deletion mutation), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**SMN1/SMN2 Dosage Analysis**

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Testing:
  o No previous genetic testing of the SMN1 gene in the carrier testing setting, or
  o Non-diagnostic results from SMN1 exon 7 deletion testing (not homozygous SMN1 deletion) in the diagnostic setting, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Index of suspicion for SMA remains high despite non-diagnostic SMN1 exon 7 deletion testing based on:
    ▪ Proximal greater than distal weakness, and
    ▪ Normal creatine kinase (CK), and
    ▪ Neurogenic EMG, OR

• Carrier Screening:
  o Have a family history of a close relative (first-, second-, or third-degree) with SMA or SMA-like disease, or
  o Have a reproductive partner who is a carrier of SMA, or
  o Have a reproductive partner with SMA, OR

• Embryos or At-Risk Fetuses:
  o SMN1/SMN2 Dosage Analysis is not suitable for preimplantation/prenatal diagnosis. Other forms of SMA testing may be indicated based on the mutation status of parents. See those sections for guidance, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

**SMN1 Known Familial Variant Analysis**

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous genetic testing for known SMN1 family mutation(s), AND

• Diagnostic Testing for Symptomatic Individuals:
  o Known family SMN1 point mutation(s) in biological relative, OR

• Carrier Screening
  o Known family SMN1 point mutation(s) in biological relative, OR

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

**SMN1 Full Gene Sequencing †**

• Genetic Counseling
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o SMN1 exon 7 deletion testing did not reveal a homozygous SMN1 deletion and SMN1/SMN2 gene dosage analysis identified a single copy of SMN1 exon 7 in the diagnostic setting, or
  o SMN1/SMN2 gene dosage analysis did not confirm carrier status of an exon 7 deletion in the carrier testing setting, AND
• Diagnostic Testing for Symptomatic Individuals:
  o Individual suspected to have compound heterozygous SMA based previous test results (see number II above) and:
    o Proximal greater than distal weakness, and
    o Normal creatine kinase (CK), and
    o Neurogenic EMG, OR
• Carrier Screening:
  o Have one of the following increased risk indication with a noninformative SMN1/SMN2 gene dosage analysis result:
    ▪ Have a reproductive partner who is a carrier of SMA, or
    ▪ Have a reproductive partner with SMA, OR
• Embryos or At-Risk Fetuses:
  o SMN1 full gene sequencing is not generally necessary for preimplantation/prenatal diagnosis as parental mutation status should have already been determined with SMN1 exon 7 deletion testing (section 1-A) +/- SMN1 known familial variant analysis (section 1-C). AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

†Lab Testing Restrictions: Previous SMN1 exon 7 deletion testing was negative

**SMN2 Gene Copy Analysis**

Genetic testing is not approved for SMN2 gene copy analysis for the purposes of predicting SMA prognosis because it is currently considered experimental, investigational or is unproven.

**References**

Spinocerebellar Ataxia

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<th>Requires:</th>
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Description

The hereditary ataxias are a group of genetic disorders characterized by a slowly progressive uncoordinated gait and often associated with poor coordination of hands, speech, and eye movements. Frequently, atrophy of the cerebellum occurs. The most common forms of hereditary ataxias are autosomal dominant, and generally show anticipation. This policy will cover the spinocerebellar ataxias (SCA), specifically SCA1, SCA2 and SCA3.1-4

Spinocerebellar ataxia’s (SCA) are an autosomal dominant set of conditions, typically affecting individuals in the fourth to fifth decade of life. The inherited SCAs are a heterogeneous group of neurologic disorders that do not allow for easy differentiation on the basis of clinical criteria alone. There are 17 recognized SCA’s with genetic testing available, although the most common SCAs are SCA1, SCA2 and SCA3, also known as Machado-Joseph Disease (MJD). SCA1 is seen in approximately 1-2 individuals per 100,000. This estimates that 6% of the worldwide ataxia population, but differs in the population. For instance, in North America SCA1 is seen in about 6% of the population5, 34% of the Serbian population6 and 22% in the Indian population7. Two studies looking at hereditary ataxia clinics found that SCA2 was seen between 13-15% of the dominant ataxia populations.5,8 In the US, SCA3 appears to affect approximately 10-20% of patients with hereditary SCA.9

All of the SCA’s have a similar presentation with progressive spinocerebellar ataxia, ocular involvement including nystagmus, slow saccadic eye movements, ophthalmoparesis or parkinsonism.1-4 In autosomal dominant conditions, the disease is typically seen in every generation. This means that an individual has a 50% chance of passing on a mutation to their children. Additionally, parents and siblings of known carriers have a 50% chance of being carriers of the same mutation. When a mutation in a child is not found in the parent, it is assumed that there is a denovo mutation in the child, or the parent has a germline mutation. Sibs would still need to be tested to rule out germline mutations.

When the gene is passed onto each generation, a phenomenon called anticipation is seen.10 This means that the gene will expand as it is passed to each generation, and tends to expand more quickly when it is passed from father to child than from mother to child. In fact, gene contractions have been seen when maternally inherited. The larger the size of the allele, the more likely it is to pass on a full expansion.
Spinocerebellar Ataxia

Genetic testing of the *ATXN1* (SCA1), *ATXN2* (SCA2) and *ATXN3* (SCA3) genes will identify 99-100% of SCA1-3 alleles. The condition is caused by a DNA expansion called a trinucleotide repeat. A trinucleotide repeat is the occurrence of the DNA nucleotides that are repeated multiple times. For the SCAs the mutation is characterized by a CAG repeat. The number of CAG DNA repeats varies among individuals and can be classified into four groups, depending on the number of repeats: normal (unaffected), mutable (intermediate), reduced penetrance and full mutation (affected status). The typical *ATXN1* (SCA1) gene has 6-44 CAG repeats. An *ATXN1* gene with 36-38 repeats is considered a mutable size. It is this range where the gene can expand or possibly contract as it is being passed on to the next generation. An allele with 39-44 repeats is within the permutation range, and anything over 44 repeats is a full mutation. SCA3 has a similar pattern with a normal allele having <44 repeats, an allele with 45-51 repeats having reduced penetrance, and 52-86 repeats being a full mutation. SCA2 alleles have a normal range of ≤31 repeats, 32-33 repeats have a later onset (after age 50) and 34+ repeats being associated with a full mutation. The use of PCR can identify up to 100 repeats. Extremely long repeats will need to be identified through Southern Blot technology.

As with other trinucleotide repeat conditions, as the number of repeats increases in individuals with SCA, the earlier the age of onset of symptoms. Anticipation can also cause an individual to appear as if they have a *denovo* mutation. A parent of an affected individual could have an expanded allele, but either died before they started showing symptoms, or the allele was not expanded to a point where they were affected. It is estimated that 95% of individuals with an SCA expansion will exhibit symptoms, although the size of the allele and age of individual will be dependent on whether symptoms will show.

The National Society of Genetic Counselors (NSGC) advocates genetic counseling for individuals and families who are undergoing genetic testing. Genetic testing to determine carrier status or confirm a diagnosis is important for reproductive information and medical management of symptoms. The NSGC does not support genetic testing for children where medical benefit is unknown. The American Society of Human Genetics/American College of Medical Genetics and Genomics (ASHG/ACMG) and the European Molecular Genetics Quality Network (EGQN) also agree that genetic testing in children for adult onset conditions should occur under specific circumstances where psychological, medical and reproductive benefits are apparent for the individual being tested.

As a result of the above guidelines, genetic testing should be approved to confirm a diagnosis or carrier status in anyone who meets clinical criteria for SCA. Additionally, genetic testing should be approved to determine the carrier status in an at risk relative with a known family mutation. Individuals who meet clinical criteria for SCA testing should be offered targeted mutation analysis. Finally, individuals with a family history of a known CAG expansion should be offered testing.

**Criteria**

Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

**Known Family Mutation for SCA**

- Genetic Counseling
Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:
- No previous genetic testing for Spinocerebellar Ataxia, AND

Diagnostic and Predisposition Testing:
- Spinocerebellar Ataxia family mutation identified in biologic relative(s), OR

Prenatal Testing:
- Spinocerebellar Ataxia family mutation identified in biologic relative(s)

**SCA Single Gene or Targeted Mutation Analysis**

- Genetic Counseling
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing for Spinocerebellar Ataxia, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Progressive cerebellar ataxia, and
  - Ocular findings, including nystagmus, slow saccadic eye movements, ophthalmoparesis or parkinsonism, OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Biologic relative(s) (1st, 2nd, or 3rd, degree) diagnosed with Spinocerebellar Ataxia clinically, and no family mutation identified, OR

**SCA Ataxia Southern Blot†**

- Genetic Counseling
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No mutation identified with Spinocerebellar Ataxia targeted mutation analysis

† **Laboratory Testing Restrictions**: Testing is authorized after no mutation identified with targeted mutation analysis

**SCA Multi-Gene Assay**

Mutation panels for multiple SCA genes, including, but not limited to, Complete Ataxia Evaluation (Athena Diagnostics), Autosomal Dominant Ataxia Evaluation (Athena Diagnostics), are **not covered.**

**References**

Tay-Sachs Disease

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<tr>
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Description

Tay-Sachs Disease (TSD) is a childhood neurodegenerative disorder caused by a buildup of a GM2 ganglioside, hexosaminidase A, in the cells, especially neurons. Multiple forms of TSD exist, including the acute infantile form, juvenile (subacute form), and chronic adult-onset forms. The acute form is characterized by progressive weakness, loss of motor skills, decreased attentiveness and increased startle reflex starting around 3-6 months. These infants usually appear normal at birth, however, the disease progresses with seizures, blindness, spasticity, and death usually by age 4. The juvenile form has a later age of onset with survival into late childhood or early adolescence. The chronic and adult-onset forms typically have a longer-term survival with slower disease progression. Typical symptoms include progressive dystonia, spinocerebellar degeneration, motor neuron disease, and in some individuals with adult-onset disease, psychosis.

TSD is found in all ethnicities and religious affiliations. Several high risk populations have been identified, including Ashkenazi Jewish, French Canadians, Cajuns from Louisiana, and Old Order Amish in Pennsylvania populations. It is estimated that approximately 1 in 30 individuals in the Ashkenazi Jewish population are carriers of TSD. Prior to extensive carrier screening in this population, TSD was seen in approximately 1 in 3600 births. Carrier screening has reduced the incidence of this disease in the Ashkenazi Jewish population by approximately 90%. The incidence of TSD in the other high risk populations is similar and sometimes higher than in the Ashkenazi Jewish population. The carrier risk in the general Caucasian populations is approximately 1 in 300.

One gene, HEXA, is associated with TSD and more than 100 mutations have been found in this gene, with several genotype/phenotype observations. Most mutations (more than 90) are associated with the acute TSD, with six mutations considered common. Three mutations are null mutations, resulting in no enzyme activity. These mutations cause the acute form of TSD, regardless of whether they are seen in a homozygous or compound heterozygous state. One of the common mutations is seen in the adult form, and two mutations cause lower levels of hexosaminidase A, but do not cause disease, and are considered pseudodeficiency alleles. Three mutations in the Ashkenazi Jewish population account for 92-98% of alleles in the heterozygote population.

Because TSD is an autosomal recessive disease, individuals usually do not have other affected family members. However, the parents of an affected individual are obligate carriers, and siblings have a 50% chance of being carriers of the condition, and a 25% chance of being affected. Offspring of the adult form
of TSD are obligate carriers and will inherit one of the two mutations in the affected individual. When testing for carrier status it is important to remember that approximately 35% of non-Jewish and 2% of Jewish heterozygotes are actually carriers of pseudodeficiency alleles.

Diagnosis of TSD can occur through HEX A enzyme analysis, targeted mutation analysis or sequence analysis of the \textit{HEXA} gene. HEX A enzyme levels can be performed to assess for carrier status or whether someone is affected with TSD. If HEX A enzyme levels are decreased, targeted analysis can confirm carrier status or test for mutations in individuals suspected to be affected. Targeted mutation analysis is typically performed by testing common mutations in the Ashkenazi Jewish population. If a targeted mutation analysis does not find a mutation(s), and an individual is suspected to be affected or has HEX A levels that suggest an individual is a carrier, sequence analysis can be performed.

Once a deleterious mutation has been identified, relatives of affected individuals can be tested. Genetic testing should be offered to at-risk family members where a germline \textit{HEXA} mutation has been identified. In addition, partners of identified carriers should be screened for their carrier status through hexosaminidase enzyme testing. If HEX A levels are low, mutation analysis can determine whether the low levels are a result of carrying a deleterious or pseudodeficiency allele. Prenatal testing is available and can be performed through HEX A enzyme levels or mutation analysis if both parental mutations are known.

Preventive use of genetic testing on a population wide basis, for any condition, may be cost-effective if genotypic information can be shown to predict disease risk. Population-wide screening is ethically justifiable only if there is an efficacious and cost-effective intervention to prevent the disorder in those who are identified as being at increase risk. At this time, population wide carrier screening for TSD is available for the following high risk populations: Ashkenazi Jewish, Cajun, French Canadian and Old Order Amish. Population screening for TSD was initiated in 1970 and is supported by the American College of Medical Genetics (ACMG) and American College of Obstetrics and Gynecology (ACOG).\textsuperscript{1,2,5}

ACMG guidelines recommend offering carrier screening to individuals of Ashkenazi Jewish descent. If only one partner is Ashkenazi Jewish, the testing of the high risk partner should occur first. Testing for the three common mutations should identify between 92-98% of carriers. Individuals whose partners are carriers should also be offered carrier screening. The offering of testing should ideally occur prior to pregnancy so that reproductive decisions can be more easily made. When testing in a prenatal setting and a pregnancy has already occurred, testing of both partners may be indicated as a result of time sensitivity. If both partners are carriers, testing should be offered to determine whether a pregnancy is affected with TSD. This can be performed either through prenatal testing (testing for HEX A enzyme levels or mutation analysis through amniocentesis or CVS) or preimplantation testing.\textsuperscript{5}

ACOG guidelines recommend testing couples of Cajun, French Canadian and Ashkenazi Jewish descent for TSD.\textsuperscript{2} If only one individual is of this high risk population, then that person should be tested first, unless a pregnancy is ongoing when both partners should be tested as a result of time sensitivity. If both partners are found to be carriers prenatal testing should be offered.

As a result of the above guidelines, it is determined that genetic testing should be approved to confirm a diagnosis or carrier status in anyone who meets clinical criteria for TSD. Individuals who have a family member with a known \textit{HEXA} mutation(s) should be tested for that/those mutation(s). Individuals from high risk populations should have targeted mutation analysis. If they test negative, they can only go on to sequencing if their family history suggests that this is necessary (i.e. a strong family history on the opposite side from the known family mutation). Individuals with low HEX A enzyme levels, who are not found to have a common mutation, should be approved to continue to sequence analysis in order to try to find a mutation(s).
Criteria
Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

**Known HEXA Family Mutation(s) Testing**

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous molecular genetic testing of HEXA, AND
- Carrier Screening:
  - Known family mutation in HEXA identified in 1st, 2nd, or 3rd degree biologic relative(s), OR
- Prenatal Testing for At-Risk Pregnancies:
  - HEXA mutation identified in both biologic parents, and
  - Pseudodeficiency allele mutation has been ruled out, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**HEXA Targeted Mutation Analysis for Common Mutations and Pseudodeficiency Alleles**

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - This same test has not been performed previously, and
  - No known HEXA mutation in family, AND
- Diagnostic Testing:
  - Abnormal or indeterminate HEX A enzymatic activity in serum, white blood cells, or other tissues, and clinical symptoms of TSD, but diagnosis remains uncertain, or
  - Asymptomatic individual with abnormal HEX A enzymatic activity in order to test for a pseudodeficiency allele, or
  - Children under the age of 6 months with
    - Progressive weakness and loss of motor skills, or
    - Decreased attentiveness, or
    - Increased startle response, or
    - Macular cherry red spot, or
    - Seizures, or
    - Blindness, or
  - Young children with
    - Ataxia and incoordination, or
    - Speech, life skills and cognition decline, or
    - Spasticity and seizures, or
    - Loss of vision, sometimes with:
      - Cherry red spot, or
      - Optic atrophy, or
• Retinitis pigmentosa, or
  o Adolescent/adult (and SMA type Kugelberg-Welander disease or early onset ALS has been ruled out) with
    ▪ Progressive dystonia, or
    ▪ Spino cerebellar degeneration, or
    ▪ Motor neuron disease, or
    ▪ Cognitive dysfunction, dementia, recurrent psychotic depression or bipolar symptoms, or
  o French Canadian, Cajun, or Old Order Amish descent regardless of symptoms, OR
• Preconception/Prenatal Carrier testing
  o Ashkenazi Jewish descent, and
  o Intention to reproduce, AND
• Carrier testing for Individuals with Family History or Partners of Carriers:
  o 1st, 2nd, or 3rd degree biologic relative with Tay-Sachs clinical diagnosis, family mutation unknown, and affected relative unavailable for testing, or
  o Partner is monoallelic or biallelic for HEXA mutation, and
  o Have the potential and intention to reproduce, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

**HEXA Full Sequence Analysis†**

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing†:
  o No mutations found on targeted mutation analysis, and
  o No previous full sequencing of HEXA, AND
• Diagnostic Testing‡:
  o Abnormal or indeterminate HEX A enzymatic activity in serum, white blood cells, or other tissues, and clinical symptoms of TSD, but diagnosis remains uncertain, OR
  o Children under the age of 6 months with one or more of the following:
    ▪ Progressive weakness and loss of motor skills,
    ▪ Decreased attentiveness
    ▪ Increased startle response
    ▪ Macular cherry red spot
    ▪ Seizures
    ▪ Blindness, or
  o Young children, with one or more of the following:
    ▪ Ataxia and incoordination
    ▪ Speech, life skills and cognition decline
    ▪ Spasticity and seizures
    ▪ Loss of vision, sometimes with:
      • Cherry red spot
      • Optic atrophy
      • Retinitis pigmentosa, or
Adolescence/adult (and SMA type Kugelberg-Welander disease or early onset ALS has been ruled out), with one or more of the following:

- Progressive dystonia
- Spinocerebellar degeneration
- Motor neuron disease
- Cognitive dysfunction, dementia, recurrent psychotic depression or bipolar symptoms, and

- Carrier testing for Individuals with Family History or Partners of Carriers:
  - 1st, 2nd, or 3rd degree biologic relative with Tay-Sachs clinical diagnosis, and family mutation unknown, and affected relative unavailable for testing, or
  - Partner is monoallelic or biallelic for a HEXA mutation, and
  - Have the potential and intention to reproduce, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**Lab Testing Restrictions:** Previous HEXA targeted mutation analysis, and no mutations found

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See LCD jurisdictions that refer to MolDX.

81255 HEXA GENE   | No                     | No                 | N/A
References

TPMT Testing

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Click here for applicable Medicare NCD/LCD information

Description

Thiopurine drugs (azathioprine, 6-mercaptopurine, thioguanine) are immunosuppressant drugs used in the treatment of hematological malignancies, autoimmune conditions, inflammatory bowel disease, and solid organ transplant rejections. Thiopurine drug toxicity can result in myelosuppression or hepatotoxicity, and can be life-threatening. These drugs are metabolized by the enzyme TPMT (thiopurine methyltransferase). Genetic variants in the TPMT gene are associated with lower enzyme activity, leading to an increased risk for drug toxicity. Product labeling for azathioprine, 6-mercaptopurine, and thioguanine and treatment guidelines from the American Gastroenterological Association recommend TPMT testing prior to initiation of thiopurine drug therapy.

Criteria

TPMT testing by phenotyping or genotyping is indicated in individuals considering treatment with any thiopurine drug:

- azathioprine (AZA, Imuran\(^*\), Azasan\(^*\))
- 6-mercaptopurine (6-MP, Mercaptopurinum\(^*\), Purinethol\(^*\))
- thioguanine (6-TG, Tabloid\(^*\), Thioguanine\(^*\))

NCD/LCD Jurisdiction and CPT Codes

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TPMT Testing

See LCD jurisdictions that refer to MolDX.

LCD: MolDX
(http://www.palmettogba.com/palmetto/MolDx.nsf/Docscat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BM/LRK6738?open&navmenu=Browse\%26By\%26Topic[||])

81401 MOPATH PROCEDURE LEVEL 2

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References

UGT1A1 Testing

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Click here for applicable Medicare NCD/LCD information

Description

Irinotecan (Camptosar®) is a chemotherapeutic drug prescribed in combination with other chemotherapy for treating metastatic and recurrent cancer of the colon or rectum. Irinotecan is a prodrug converted to an active form by carboxylesterase enzymes in the liver. Elimination of the active form is dependent on the hepatic enzyme uridine diphosphate glucuronosy transferase 1 (UGT1A1). A common variant in this gene can cause reduced enzyme activity, leading to a buildup of drug metabolites resulting in neutropenia. The FDA label for irinotecan states that people found to have two copies of the UGT1A1*28 variant require lower doses to avoid toxicity.

Criteria

UGT1A1 testing is indicated in individuals with metastatic and/or recurrent colorectal cancer prior to the initiation of irinotecan therapy.

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81350 UGT1A1 GENE No No No

VA, NC, SC, WV


81350 UGT1A1 GENE No No Yes

See LCD jurisdictions that refer to MolDX.

LCD: MolDX (http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Excluded%20Tests~92WUWD6087?open&navmenu=Browse%5CnBy%5CTopic%5CI)

81350 UGT1A1 GENE No No N/A

References

UroVysion

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Description

Bladder cancer is one of the most common types of cancer in the U.S., especially among men. Urothelial carcinoma (UC) accounts for most cases of bladder cancer. Most cases of UC are low-grade and easily treated. However, UC has a high risk of recurrence (70%), and patients must be monitored for several years after treatment. Diagnostic monitoring usually consists of regular testing of cells in the urine (cytology).

UroVysion® FISH (fluorescence in situ hybridization) testing is an alternative to cytology. UroVysion testing detects extra or missing chromosomes 3, 7 or 17 and gene changes to a piece of chromosome 9 often found in UC patients.

UroVysion testing is FDA approved but its use is not endorsed by current clinical guidelines. The American Urological Association (AUA) guidelines for diagnosis and management of bladder cancer state that techniques like UroVysion "hold promise" in future assessment of risk, prognosis, and targeted treatment, but do not currently recommend such testing. National Comprehensive Cancer Network (NCCN) guidelines do not address UroVysion or other FISH testing for bladder cancer.

Criteria

UroVysion testing is considered investigational at this time and is not routinely indicated.

References

Von Hippel-Lindau Disease

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* - Clinical Review necessary prior to authorization for this procedure.
† - Lab procedures require specified sequence to be followed and additional information is required to be supplied by lab performing procedure(s).

Description

Von Hippel-Lindau Disease (VHL) is an inherited familial cancer syndrome with an autosomal dominant inheritance pattern. It is characterized by hemangioblastomas of the brain, spinal cord, and retina; renal cysts and renal cell carcinoma; pheochromocytoma; pancreatic cysts and neuroendocrine tumours; endolymphatic sac tumors; and epididymal and broad ligament cysts.1,2

VHL can be subdivided into two types based on pheochromocytoma risk: type 1 and type 2. Type 1 VHL has a low risk of developing a pheochromocytoma, whereas type 2 has a high risk for developing pheochromocytoma. Type 2 can be further subdivided into a low risk (2A) or high risk (2B) of developing renal cell carcinoma. Type 2C develops pheochromocytomas exclusively, without risk of carcinomas.1

The incidence of VHL is approximately 1 in 36,000 and has a 90% penetrance by age 65.1 About 80% of individuals diagnosed with VHL disease have an affected parent. De novo mutations of VHL are estimated to occur in about 20% of probands.1 VHL is inherited in an autosomal dominant manner.1,2

Sequence analysis of VHL detects approximately 72% of mutations.1 Most mutations are small intragenic deletions/insertions, missense, nonsense, and splice-site mutations that can be identified through sequencing. Partial or whole-gene deletions can be detected by deletion/duplication analysis which will detect an additional 28% of disease-causing mutations.

Genetic testing may be more complicated in those with no family history of VHL. In such cases, the new mutation may have arisen later in development, causing mosaicism in cells and tissues. Therefore, an individual may have clinical features of VHL, but test negative for a gene mutation. Since mosaicism can occur in the somatic tissue, germline tissue, or both, the risks to the carrier and to his/her children can differ based on the level and extent of mosaicism.1,3

The American Society of Clinical Oncology (ASCO) recommends that genetic testing be offered when 1) the individual has a family or personal history suggestive of a familial cancer syndrome, 2) the test can be adequately interpreted, and 3) the results will help medical management.4,5

As a result of the above general guidelines, CareCore has determined that genetic testing should be approved to confirm a diagnosis in anyone who meets clinical criteria for VHL. Some individuals do not have a family history and therefore need to meet more stringent clinical criteria to be eligible for genetic testing.
testing. Additionally, genetic testing should be approved to determine carrier status in an at risk relative with a known genetic mutation. Because early detection of at-risk individuals affects medical management, testing of asymptomatic individuals during childhood is beneficial.1,4

Individuals who have a family member with a known VHL mutation should be tested for that mutation. Individuals who meet clinical criteria for VHL should be offered sequence analysis. If sequence analysis is negative, deletion/duplication testing should be offered.

Criteria
Requests for testing will be authorized if the following criteria are met. Requests not meeting the criteria will result with a medical review of the case.

Known VHL Family Mutation Testing †

- Genetic Counseling
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous VHL gene testing that would have detected the family mutation, AND
- Diagnostic and Predisposition Testing*:
  - Known family mutation in VHL identified in 1st degree relative(s). (Note: 2nd or 3rd degree relatives may be considered when 1st degree relatives are unavailable or unwilling to be tested), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

†Lab testing restrictions: Testing is authorized for known family mutation(s) only.
* Includes prenatal testing for at-risk pregnancies.

Full Sequence Analysis of VHL

- Genetic Counseling
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous VHL gene sequencing, and
  - No known familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
  - A positive family history of VHL, and
    - Spinal or cerebellar hemangioblastoma, or
    - Retinal hemangioblastoma, or
    - Renal cell carcinoma, or
    - Pheochromocytoma, or
    - Multiple renal and/or pancreatic cysts, or
  - No known family history of VHL-related findings, and
- Two or more hemangioblastomas involving the retina, spine, and/or brain, or
- A single hemangioblastoma and a characteristic visceral mass (such as renal cell carcinoma, pheochromocytoma, endolymphatic sac tumors, papillary cystadenomas of the epididymis or broad ligament, or neuroendocrine tumors of the pancreas), OR

- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - A first-degree relative of someone with a clinical diagnosis of VHL who has had no previous genetic testing (Note that testing in the setting of a more distant affected relative will only be considered if the first-degree relative is unavailable or unwilling to be tested); AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

**Deletion/Duplication Analysis of VHL†**

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - There is no known familial mutation, and
  - No previous deletion/duplication analysis of the VHL gene has been performed, and
  - Above criteria for VHL full gene sequence analysis are met, and
  - VHL sequencing was previously performed and no mutations were found, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

†Lab Test Restrictions: Previous VHL sequencing performed and no mutations found

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<td>adenoma</td>
<td>An ordinarily benign neoplasm of epithelial tissue. If an adenoma becomes cancerous, it is known as an adenocarcinoma.</td>
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<td>adenomatous polyposis coli</td>
<td>Adenomatous polyposis coli (APC) is a gene located on chromosome 5q. Inherited APC gene mutations are associated with Familial Adenomatous Polyposis (FAP) and Attenuated FAP. Most colorectal cancer polyps have mutations in both copies of the APC gene, even in people that don’t have FAP.</td>
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<td>adjuvant therapy</td>
<td>When discussing cancer treatment, adjuvant therapy is given after a primary treatment (like surgery) to increase the chances of a cure. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, or biological therapy.</td>
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<td>adverse drug reaction</td>
<td>A harmful or unpleasant reaction to a drug that generally means the drug should be prescribed differently or avoided.</td>
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<td>aerobic exercise</td>
<td>Any physical activity that causes the heart to pump faster and harder and breathing to quicken. Strengthens the heart muscle and may also help lower high blood pressure and increase good cholesterol.</td>
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<td>Attenuated FAP (AFAP) is a form of FAP characterized by a less dramatic proliferation of polyps (between 20-99 cumulative polyps) and age of onset for colorectal cancer of approximately 50 years. Polyps generally localize to the proximal (right-sided) colon. The American Gastroenterological Association (AGA) recommends genetic testing once a person has developed 20 or more cumulative polyps.</td>
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<td>Short for “alpha-fetoprotein”, a substance found in pregnant women’s blood. High levels of AFP are associated with risk for spina bifida and abdominal wall defects.</td>
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<td>The protective fluid that surrounds the developing baby. This fluid fills the amniotic sac, or “bag of water” inside the mother’s uterus.</td>
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<td>Can be represented by a family tree showing how biological family members are related to each other. It is sometimes used interchangeably with “lineage.”</td>
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<td>A condition caused by too little oxygen in the blood, usually caused by too little hemoglobin or too few red blood cells.</td>
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<td>angina</td>
<td>Pain, pressure, or a feeling of indigestion in the chest caused by too little oxygen-rich blood reaching the heart. Usually caused by coronary artery disease.</td>
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<td>anticipation</td>
<td>A way certain genetic diseases are inherited that causes them to get worse over the generations.</td>
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<td>Medications that prevent the blood from clotting -- often call “blood thinners.”</td>
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<td>Medications used to prevent or treat seizures. Common anticonvulsant drugs include Dilantin, Zantoin, Klonopin, Valium, Tegretol, Depakote and others.</td>
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<td>A medication used to prevent or treat depression. Current antidepressants categories include SSRIs, MAOIs, tricyclics, tetracyclics, and others.</td>
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<tr>
<td>antipsychotic</td>
<td>Medications used to treat schizophrenia, schizoaffective disorder, bipolar disorder and other conditions that distort a person’s grasp of reality.</td>
</tr>
<tr>
<td>antiretroviral</td>
<td>A medication used to treat a retrovirus infection, such as HIV</td>
</tr>
<tr>
<td>APOB</td>
<td>A gene for the protein that normally helps deliver LDL cholesterol to the liver to be broken down. An APOB gene mutation causes a person not to clear LDL from the body as well as usual and it builds up. APOB mutations are one cause of familial hypercholesterolemia, although LDLR mutations are the most common.</td>
</tr>
<tr>
<td>Apolipoprotein B100</td>
<td>ApoB100 is short for apolipoprotein B100. It is a normal protein that is a major part of &quot;bad&quot; cholesterol. High ApoB100 is a strong risk factor for heart disease.</td>
</tr>
<tr>
<td>aromatase inhibitor</td>
<td>A class of drugs used to treat postmenopausal women who have hormone-dependent breast cancer. Ais work by blocking the enzyme aromatase responsible for converting androgen to estrogen. This limits the amount of estrogen available to promote breast cancer growth.</td>
</tr>
<tr>
<td>arrhythmia</td>
<td>Any variation from the normal heart rate or rhythm. The heart might beat faster than usual (tachycardia), slower than usual (bradycardia), or with an unusual pattern.</td>
</tr>
<tr>
<td>artery</td>
<td>Blood vessels that carry oxygen-rich blood throughout the body. The coronary arteries carry blood to the heart muscle.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Ashkenazi Jewish</strong></td>
<td>Jewish people whose ancestors are from Eastern Europe -- mostly Germany, Poland, Russia, and some parts of France. Whereas Sephardic Jewish people have ancestry from Spain, Portugal, parts of France, Italy, North Africa, and the Middle East. Most American Jews are Ashkenazi.</td>
</tr>
<tr>
<td><strong>atherosclerosis</strong></td>
<td>A disease caused by plaque buildup inside the arteries that limits blood flow. Also called hardening of the arteries.</td>
</tr>
<tr>
<td><strong>autosomal dominant</strong></td>
<td>A pattern of inheritance where only one gene from a pair isn’t working properly and causes the condition. Anyone with an autosomal dominant condition has a 50% chance of passing on the nonworking gene -- and, therefore, the condition -- to each child.</td>
</tr>
<tr>
<td><strong>autosomal recessive</strong></td>
<td>Describes a pattern of inheritance where both genes from a pair must be working abnormally to cause the condition. People with one abnormal and one normally working gene don't have the condition and are called carriers. When both parents are unaffected carriers of a condition, there is a 25% chance to have an affected child with each pregnancy.</td>
</tr>
<tr>
<td><strong>average woman</strong></td>
<td>The &quot;average woman&quot; is someone picked at random from the general public.</td>
</tr>
<tr>
<td><strong>Beta-thalassemia</strong></td>
<td>An inherited blood disorder that causes anemia, which is a shortage of red blood cells. This disorder causes lower than usual amounts of oxygen in the blood.</td>
</tr>
<tr>
<td><strong>b-hCG</strong></td>
<td>Short for &quot;beta-human chorionic gonadotropin&quot;, this substance is known as the pregnancy hormone. It is produced by the placenta.</td>
</tr>
<tr>
<td><strong>biopsy</strong></td>
<td>The process of removing tissue from living patients for diagnostic evaluation.</td>
</tr>
<tr>
<td><strong>black box warning</strong></td>
<td>A warning required by the U.S. Food and Drug Administration (FDA) on the package inserts of some prescription drugs. These are the strongest warnings from the FDA about a significant risk for serious or life-threatening complications of a drug. Black box refers to the heavy black line surrounding the warning.</td>
</tr>
<tr>
<td><strong>blood clot</strong></td>
<td>Proteins change liquid blood into a solid blood clot usually in response to an injury to prevent further blood loss. Imbalance in the clotting proteins can lead to too little or too much clotting (thrombosis). When an abnormal clot forms, it can block blood flow and cause tissue damage or death.</td>
</tr>
<tr>
<td><strong>blood clotting factor</strong></td>
<td>Proteins and enzymes in the blood that control changing liquid blood into a solid blood clot. Imbalance of these factors can cause too little or too much clotting.</td>
</tr>
<tr>
<td><strong>blood transfusion</strong></td>
<td>Transferring blood or components of blood, such as blood plasma, into a patient.</td>
</tr>
<tr>
<td><strong>blood vessel</strong></td>
<td>The channels that carry blood throughout the body: arteries, veins and capillaries</td>
</tr>
<tr>
<td><strong>bone marrow transplant</strong></td>
<td>A procedure that replaces diseased or damaged bone marrow with healthy bone marrow. The damaged bone marrow may be destroyed by chemotherapy or radiation. The healthy bone marrow can come from the patient or a donor.</td>
</tr>
<tr>
<td><strong>bowel preparation</strong></td>
<td>Purging and cleansing of the bowel of fecal and other matter to assure clear evaluation of the bowel.</td>
</tr>
<tr>
<td><strong>BRCA1</strong></td>
<td>A gene located on chromosome 17 that normally produces a protein to help restrain cell growth. A harmful change in BRCA1 may predispose a person toward developing breast and/or ovarian cancer.</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td>A gene located on chromosome 13 that normally produces a protein to help to restrain cell growth. A harmful change in BRCA2 may predispose a person toward developing breast and/or ovarian cancer.</td>
</tr>
<tr>
<td><strong>breast MRI</strong></td>
<td>MRI uses powerful magnets and radio waves to create detailed pictures of the breast and surrounding tissues. It provides clear pictures of parts of the breast that are difficult to see clearly on ultrasound or mammogram, but it's not a replacement for mammography.</td>
</tr>
<tr>
<td><strong>cancer</strong></td>
<td>A disease where abnormal cells grow and divide without control. Cancer cells can invade nearby tissues and spread through the bloodstream and lymphatic system to other parts of the body (called metastasis).</td>
</tr>
<tr>
<td><strong>carbohydrate</strong></td>
<td>Carbohydrates are the most abundant nutrients we eat and are broken down by the liver into glucose (sugar) to provide energy.</td>
</tr>
<tr>
<td><strong>carcinoma</strong></td>
<td>A cancer that begins in the skin or tissues that line or cover internal organs.</td>
</tr>
<tr>
<td><strong>cardiomyopathy</strong></td>
<td>A heart muscle disease that usually leads to a weakened heart muscle and a reduced ability to pump blood effectively. Any damage to the heart muscle can cause cardiomyopathy. Recognized causes include genetic factors, heart attack, alcoholism, and certain viral infections.</td>
</tr>
<tr>
<td><strong>carrier</strong></td>
<td>A person who has one copy of a changed gene and one normal copy of that gene.</td>
</tr>
<tr>
<td><strong>CBC</strong></td>
<td>An abbreviation for &quot;complete blood count&quot;. A standard test that provides information including the white blood cell count, red blood cell count, amount of hemoglobin, platelet count and more.</td>
</tr>
<tr>
<td>Term</td>
<td>Description</td>
</tr>
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</tr>
<tr>
<td>CCR5-tropic</td>
<td>A form of HIV virus that uses a protein on the outside of a cell, called the CCR5 receptor, to enter and infect the cell.</td>
</tr>
<tr>
<td>CD4 cells</td>
<td>A kind of white blood cell, also called “helper T cells”, which help protect the body against infection. These are the cells that the HIV virus infects.</td>
</tr>
<tr>
<td>cell</td>
<td>The basic building block of the tissues and organs in the body. Most cells have a complete copy of our genetic code and all cells are made by copying existing cells.</td>
</tr>
<tr>
<td>chelation therapy</td>
<td>Treatment to remove iron from the body using a chemical that attaches to heavy metals inside the body to remove them.</td>
</tr>
<tr>
<td>chemoprevention</td>
<td>The administration of any chemical or drug to treat a disease or condition and limit its further progress, or to prevent the condition from ever occurring.</td>
</tr>
<tr>
<td>cholesterol</td>
<td>A waxy, fat-like substance used by the body to make hormones, vitamin D, and other important substances. Eating too much cholesterol increases the risk of heart disease.</td>
</tr>
<tr>
<td>chromosome</td>
<td>A threadlike strand of DNA that carries genes and transmits hereditary information. Each chromosome can contain hundreds or thousands of individual genes. The number of chromosomes in the normal human cell is 46 (23 pairs).</td>
</tr>
<tr>
<td>chromosome translocation</td>
<td>An genetic condition where material from one chromosome breaks off and sticks to another chromosome, or switches places with a part of another chromosome. There are different types of translocations, and they can have different effects on health and development.</td>
</tr>
<tr>
<td>CHRPE</td>
<td>Congenital Hypertrophy of Retinal Pigmented Epithelium - a benign eye abnormality common in those with FAP.</td>
</tr>
<tr>
<td>close relative</td>
<td>A close relative is defined as a mother, father, sister, brother or child.</td>
</tr>
<tr>
<td>colectomy</td>
<td>The surgical removal of the colon. A total colectomy is the surgical removal of the colon and rectum. A subtotal colectomy is the surgical removal of the colon or portions of the colon only (not rectum).</td>
</tr>
<tr>
<td>colon</td>
<td>Another name for the large intestine; the section of the large intestine extending from the cecum to the rectum. An adult colon is approximately five to six feet in length and is responsible for absorbing water and forming, storing, and expelling waste.</td>
</tr>
<tr>
<td>colonoscopy</td>
<td>A procedure that examines the entire rectum and colon. A colonoscopy is a long, flexible, lighted tube with a tiny lens on the end used to directly examine the whole colon and look for the presence of growths. Colonoscopy is the most effective way to evaluate the inside of your entire colon for the presence of colorectal cancer or polyps. This procedure is considered “invasive,” because it requires sedation and the insertion of the colonoscope through the rectum.</td>
</tr>
<tr>
<td>colorectal cancer</td>
<td>Cancer that occurs in the rectum or the colon.</td>
</tr>
<tr>
<td>Comprehensive Analysis</td>
<td>Comprehensive Analysis is the most complete BRCA test. It looks at all the coding DNA of the BRCA1 and BRCA2 genes, to see if there are any changes or mutations. It can find: changes that are known to cause cancer, changes that are harmless, and changes whose link to cancer is unknown.</td>
</tr>
<tr>
<td>congenital heart defect</td>
<td>A problem with the structure of the heart, or the vessels connected to it, which is present from birth. Many types of heart defects exist. They can affect how the blood flows through the heart, or its rhythm.</td>
</tr>
<tr>
<td>corneal arcus</td>
<td>Also called “arcus cornealis”. An accumulation of cholesterol around the cornea (the clear front surface of the eye) that causes a grey ring around the colored part of the eye. May be a normal feature of aging, but may also be a sign of unusually high cholesterol levels.</td>
</tr>
<tr>
<td>CXCR4-tropic</td>
<td>A form of HIV virus that uses a protein on the outside of a cell, called the CXCR4 receptor, to enter and infect the cell.</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>An enzyme involved in the metabolism of many drugs, including caffeine. Some people have a form of CYP1A2 that is particularly susceptible to tobacco smoke and may have adverse reactions when taking drugs metabolized by CYP1A2 while smoking.</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>An enzyme involved in the metabolism of many drugs, including several ulcer and reflux drugs. Variants in the gene can cause adverse reactions to drugs metabolized by CYP2C19.</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>An enzyme involved in the metabolism of many drugs, including warfarin and celecoxib. and several anti-inflammatory. Variants in the gene can cause adverse reactions to drugs metabolized by CYP2C9.</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>An enzyme involved in the metabolism of many drugs, including codeine, tamoxifen, and several antidepressants. Variants in the gene can cause adverse reactions to drugs metabolized by CYP2D6.</td>
</tr>
<tr>
<td>cytochrome P450</td>
<td>Cytochrome P450, abbreviated CYP450, is a large family of drug metabolizing enzymes, including CYP1A2, CYP2C9, CYP2C19, and CYP2D6.</td>
</tr>
<tr>
<td>de novo mutation</td>
<td>A mutation that is not running in the family yet, but occurs when a gene is damaged at conception. A de novo mutation can also then be passed on to one's children.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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</tr>
<tr>
<td>Desmoid tumor</td>
<td>Fibrous growth identified generally in the abdominal area associated with FAP and AFAP.</td>
</tr>
<tr>
<td>detection rate</td>
<td>Also called &quot;sensitivity&quot;. Refers to the likelihood that a test will actually find the condition that it is looking for. If a test has a 90% detection rate, it will find 90% (9 out of 10) of people with the condition. Most tests don't have a 100% detection rate, so you should pay attention to detection rates to understand the limitations of any test you consider.</td>
</tr>
<tr>
<td>diabetes</td>
<td>A disease that causes you to have too much glucose (sugar) in your blood because of a problem with the hormone insulin. People with diabetes either can't make insulin (type I) or they can't use it well enough (type II).</td>
</tr>
<tr>
<td>DNA</td>
<td>Stands for &quot;deoxyribonucleic acid&quot;. The chemical inside the nucleus of the cell that encodes the genetic instructions passed from generation to generation. Genes are made of DNA.</td>
</tr>
<tr>
<td>DNA replication</td>
<td>The duplication process of genetic material.</td>
</tr>
<tr>
<td>drug interaction</td>
<td>When a drug reacts with another drug (prescribed, over-the-counter, herbs, supplements, etc.), food, or other environmental exposure to cause an altered response. The effect may be an increased or decreased response or an adverse drug reaction.</td>
</tr>
<tr>
<td>environment</td>
<td>When talking about what causes disease, environment refers to basically everything that isn't controlled by genetics. Environment can include what we eat, physical activity, medications we take, chemicals we are exposed to, our physical surroundings, and countless other factors.</td>
</tr>
<tr>
<td>enzyme</td>
<td>A protein made by the body that encourages a biochemical reaction. Humans make hundreds of different enzymes from the instructions in our genes. If any one enzyme isn't working normally, it can cause a disease.</td>
</tr>
<tr>
<td>epithelium</td>
<td>Membranous tissue constructed of one or more layers of cells that cover the internal and external surfaces of the body and its organs.</td>
</tr>
<tr>
<td>ethnic background</td>
<td>The geographical and racial identity of a person's ancestors</td>
</tr>
<tr>
<td>ethnic group</td>
<td>A group of people whose ancestors lived in the same region of the world, and thus, who share a common genetic background</td>
</tr>
<tr>
<td>ethnicity</td>
<td>A group of people who frequently share some common ancestry and are, therefore, more likely to share certain genetic traits or mutations. May be based on descending from the same geographical location, a shared religion, a tribal connection, or other cultural practices. People often belong to more than one ethnic group.</td>
</tr>
<tr>
<td>extensive metabolizer</td>
<td>Extensive metabolizers have two &quot;normal&quot; drug metabolism genes. They make the average amount of enzyme and usually have normal drug response. Most people are extensive metabolizers. People have many drug metabolism genes and can be different kinds of metabolizers for each.</td>
</tr>
<tr>
<td>false negative</td>
<td>A test result that is read as negative when the disease is present.</td>
</tr>
<tr>
<td>false positive</td>
<td>A test result that is read as positive when the disease is not present.</td>
</tr>
<tr>
<td>familial adenomatous</td>
<td>Familial Adenomatous Polyposis (FAP) is an inherited condition that causes the formation of hundreds to thousands of precancerous polyps within the colon, often before age 20. FAP is usually caused by an inherited mutation in one copy of the APC gene.</td>
</tr>
<tr>
<td>polyposis</td>
<td>An inherited condition that causes people to have very high levels of LDL, or &quot;bad&quot;, cholesterol and a high risk for heart disease if not aggressively treated with cholesterol-lowering drugs.</td>
</tr>
<tr>
<td>family history</td>
<td>Family history may refer to whether or not you have any biological relative with a specific condition. It may also refer to the collective medical histories of all of your biological relatives. An accurate family history is one of the most important tools available to predict and prevent conditions that you may be at risk for.</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration, a department of the federal government, that regulates drugs, foods, some tests, medical devices, and other things that may impact public health and safety.</td>
</tr>
<tr>
<td>fecal immunochemical</td>
<td>Fecal immunochemical test (FIT) is a test, similar to FOBT, to check for hidden blood in the stool. Blood may signal cancer or one of many non-cancer related causes of bleeding.</td>
</tr>
<tr>
<td>test</td>
<td>Fecal occult blood test (FOBT) is a test to check for hidden blood in the stool. The presence of blood in stool may be a sign of cancer or one of the many non-cancer related causes of bleeding (e.g. hemorrhoids).</td>
</tr>
<tr>
<td>fibrate</td>
<td>A group of drugs that work to lower your &quot;bad&quot; (LDL) cholesterol by reducing your triglycerides (another type of fat) and raising your &quot;good&quot; (HDL) cholesterol. Commonly prescribed fibrates include fenofibrate (brand name examples include: Antara, Fenoglide, Lipofen, Lofibra, TriCor, Triglide, and Lipidil) and gemfibrozil (brand name: Lopid).</td>
</tr>
<tr>
<td><strong>flexible sigmoidoscopy</strong></td>
<td>Procedure used to examine the rectum and lower third of the colon. A sigmoidoscope is a long, flexible, slender tube with a lens on the end used to visualize a portion of the colon to look for the presence of growths.</td>
</tr>
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</tr>
<tr>
<td><strong>functional</strong></td>
<td>Functional refers to genes or proteins that are not affected by genetic changes that disrupt their normal structure or behavior.</td>
</tr>
<tr>
<td><strong>gastrointestinal tract</strong></td>
<td>The digestive system, consisting of the esophagus, stomach, small intestine and large intestine.</td>
</tr>
<tr>
<td><strong>gene</strong></td>
<td>A piece of DNA that acts as an instruction to the body for how to make a specific protein (enzyme, hormone, etc.). Genes are inherited, passed from parent to child.</td>
</tr>
<tr>
<td><strong>gene sequencing</strong></td>
<td>A genetic test that is considered the gold standard for finding genetic changes known as mutations.</td>
</tr>
<tr>
<td><strong>genetic</strong></td>
<td>Refers to any trait that is inherited, or passed from generation to generation through genes. These traits may range from having specific diseases to our response to certain drugs to simply our physical characteristics, like eye and hair color.</td>
</tr>
<tr>
<td><strong>genetic condition</strong></td>
<td>A genetic condition is any disease, disorder, syndrome, or trait that is caused, at least in part, from alterations in genes or chromosomes.</td>
</tr>
<tr>
<td><strong>genetic counseling</strong></td>
<td>Genetic counseling is a process to help people learn about, cope with, and manage their risk of genetic disorders. This risk may be uncovered because the person is diagnosed with a condition, has a family history, has an affected child, and/or has an abnormal genetic test result.</td>
</tr>
<tr>
<td><strong>genetic counselor</strong></td>
<td>A healthcare professional with specialized training in how the science of genetics relates to medical care. A genetic counselor can evaluate your personal and family history, identify any risk factors for birth defects or genetic conditions, and help you understand and make decisions about testing or other options you may have.</td>
</tr>
<tr>
<td><strong>genetic discrimination</strong></td>
<td>Treatment or consideration based on genetic status or category rather than individual merit or actual conditions.</td>
</tr>
<tr>
<td><strong>genetic modifier</strong></td>
<td>A gene that changes how another gene is expressed.</td>
</tr>
<tr>
<td><strong>genetic predisposition</strong></td>
<td>Any condition in which genetic make-up leaves the individual more susceptible to disease.</td>
</tr>
<tr>
<td><strong>genetic test</strong></td>
<td>A specific type of laboratory test that is designed to find out if a person has a genetic disorder, is a carrier of a genetic disease, or has a predisposition to develop a genetic problem. Genetic testing can look at chromosomes, genes, or proteins -- depending on the specific condition being tested.</td>
</tr>
<tr>
<td><strong>genomics</strong></td>
<td>The study of the genome and its significance to pathology and disease.</td>
</tr>
<tr>
<td><strong>genotype</strong></td>
<td>The version of genes a person, organism, or cancer has.</td>
</tr>
<tr>
<td><strong>genotyping</strong></td>
<td>Tests that look specifically at the genetic information of a person, organism, or cancer. These tests may predict a certain characteristic (&quot;phenotype&quot;) but don't actually test for that characteristic.</td>
</tr>
<tr>
<td><strong>glucose</strong></td>
<td>A form of sugar made from carbohydrates we eat that the body uses for energy. Too much glucose in their blood may be a sign of diabetes.</td>
</tr>
<tr>
<td><strong>HBB</strong></td>
<td>A gene involved in making a piece of a protein called hemoglobin. Genetic changes, or mutations, in the HBB gene can cause sickle cell disease and beta-thalassemia.</td>
</tr>
<tr>
<td><strong>HDL</strong></td>
<td>High density lipoprotein cholesterol. Also called the &quot;good&quot; cholesterol. High HDL lowers the risk for heart disease.</td>
</tr>
<tr>
<td><strong>HDL2</strong></td>
<td>A subtype of HDL (the &quot;good&quot; cholesterol). HDL2 is the &quot;best&quot; cholesterol because high levels give you the most protection against heart disease -- even more than just high total HDL.</td>
</tr>
<tr>
<td><strong>HDL3</strong></td>
<td>A subtype of HDL (the &quot;good&quot; cholesterol). HDL3 is not as good for you as other types of HDL. Some studies show that high levels of HDL3 may actually increase your risk for heart disease.</td>
</tr>
<tr>
<td><strong>heart</strong></td>
<td>A muscular organ whose primary job is to pump blood to all parts of the body.</td>
</tr>
<tr>
<td><strong>heart attack</strong></td>
<td>When the blood supply to part of the heart muscle is suddenly blocked. The heart muscle may be damaged or start to die if blood doesn't return quickly.</td>
</tr>
<tr>
<td><strong>heart disease</strong></td>
<td>A general term for any condition that threatens the heart's ability to function normally. Because coronary artery disease (plaque buildup that may cause a heart attack) is by far the most common type, it is often just called heart disease.</td>
</tr>
<tr>
<td><strong>hemochromatosis</strong></td>
<td>A condition in which too much iron builds up in the body, which can lead to organ damage.</td>
</tr>
<tr>
<td><strong>hemoglobin</strong></td>
<td>A protein found in red blood cells that carries oxygen throughout the body.</td>
</tr>
<tr>
<td><strong>hemoglobin analysis</strong></td>
<td>A test that measures the different types of hemoglobin in the blood. It is used to diagnose diseases caused by abnormal hemoglobin, such as sickle cell anemia.</td>
</tr>
<tr>
<td><strong>hereditary</strong></td>
<td>Genetically transmitted -- or capable of being transmitted -- from parent to child.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>hereditary nonpolyposis colorectal cancer</td>
<td>Hereditary non-polyposis colorectal cancer (HNPCC) is an inherited disorder in which there is a tendency to develop colorectal cancer without a significant number of polyp precursors. HNPCC is specifically associated with inherited mutations in five mismatch repair genes.</td>
</tr>
<tr>
<td>HFE gene</td>
<td>The HFE gene makes a protein that regulates how much iron your body absorbs from your diet.</td>
</tr>
<tr>
<td>high performance liquid chromatography</td>
<td>A laboratory procedure that can separate a liquid mixture into its individual compounds. As an example, this procedure is used to separate different kinds of hemoglobins in a person's blood.</td>
</tr>
<tr>
<td>HNPCC-related cancer</td>
<td>Other primary cancers included in an inherited cancer syndrome because of the increased prevalence in syndrome carriers. In addition to colon cancer, HNPCC-related cancers include cancer of the endometrium, ovary, stomach, kidney/urinary tract, brain, biliary tract, central nervous system and small bowel.</td>
</tr>
<tr>
<td>hormone</td>
<td>Chemical messengers made mostly in our glands that influence our growth and development, sexual function, reproduction, mood, and metabolism. Hormone medications include oral contraceptive pills, patches or rings; hormonal treatments for infertility; hormone replacement therapy; or serum estrogen modifiers (sometimes taken to treat or prevent certain forms of cancer).</td>
</tr>
<tr>
<td>human immunodeficiency virus</td>
<td>A retrovirus that attacks the human immune system, thus affecting the body's ability to fight off the organisms that cause disease. HIV is the cause of acquired immune deficiency syndrome or AIDS.</td>
</tr>
<tr>
<td>hypertension</td>
<td>Blood pressure that stays at 140/90 mmHg or higher over a period of time. Average blood pressure is about 120/80 mmHg.</td>
</tr>
<tr>
<td>IDL</td>
<td>Intermediate density lipoprotein -- a type of &quot;bad&quot; cholesterol. High IDL increases the risk for heart disease even more than just high total LDL levels. IDL is under strong genetic control so close relatives of someone with high IDL should also consider testing.</td>
</tr>
<tr>
<td>in vitro fertilization</td>
<td>A laboratory procedure in which sperm fertilize eggs outside the body in a laboratory setting to facilitate pregnancy. The fertilized egg is then placed in the woman's uterus for implantation.</td>
</tr>
<tr>
<td>inherited</td>
<td>Any trait that is passed from generation to generation through our genes. These traits may range from having a specific disease to how we respond to certain drugs to simply our physical characteristics, like eye and hair color.</td>
</tr>
<tr>
<td>inhibin A</td>
<td>A substance made by the placenta during pregnancy and found in the mother's blood. Also abbreviated “DIA.”</td>
</tr>
<tr>
<td>insulin</td>
<td>A hormone that helps glucose, the sugar used by the body for energy, get into the cells that need it. When you don't make enough insulin or you can't use insulin effectively, you are likely to develop diabetes.</td>
</tr>
<tr>
<td>intermediate metabolizer</td>
<td>Intermediate metabolizers have a drug metabolism gene that doesn't work properly. They make less of the enzyme coded for by those genes, but usually make enough to process most drugs. People have many drug metabolism genes and can have be different kinds of metabolizers for each.</td>
</tr>
<tr>
<td>iron overload</td>
<td>A condition in which higher-than-usual amounts of iron collect in the tissues of the body. Over time, iron overload can damage organs like the liver and cause problems like diabetes.</td>
</tr>
<tr>
<td>K-RAS</td>
<td>A gene that when mutated contributes to converting a normal cell into a cancerous cell.</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein cholesterol. Also called the &quot;bad&quot; cholesterol. High LDL increases the risk of heart disease.</td>
</tr>
<tr>
<td>LDLR</td>
<td>Stands for low density lipoprotein receptor. The LDLR gene normally makes a protein that helps to remove LDL (bad cholesterol) from the blood. An LDLR gene mutation causes a person not to get rid of LDL as quickly and it builds up. LDLR mutations are the most common cause of familial hypercholesterolemia.</td>
</tr>
<tr>
<td>leukemia</td>
<td>A cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the bloodstream.</td>
</tr>
<tr>
<td>lifestyle</td>
<td>In talking about health conditions, lifestyle generally refers to factors within your control like diet, physical activity, smoking, alcohol use, and use of other preventive health measures.</td>
</tr>
<tr>
<td>lipid</td>
<td>A fat that acts as a source of energy and helps the body use certain vitamins. Cholesterol and triglycerides are examples of lipids. High lipid levels increase the risk for heart disease and diabetes and may be caused by eating too much fat, alcohol use, inactivity, inherited conditions, and certain medications and disease.</td>
</tr>
<tr>
<td>lipoprotein a</td>
<td>Lp(a) stands for lipoprotein a -- a type of &quot;bad&quot; cholesterol. High Lp(a) increases the risk of heart disease 2 to 10 times more than just high total LDL levels and may cause heart disease earlier than usual. Drug therapy is usually needed. Lp(a) is under strong genetic control so close relatives of someone with high Lp(a) should also consider testing.</td>
</tr>
<tr>
<td>liver</td>
<td>An organ involved in a wide range of functions, including helping with digestion and the detoxification of chemicals.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>---------------------------</td>
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</tr>
<tr>
<td>liver biopsy</td>
<td>A surgical procedure that removes a small piece of liver so it can be examined in a lab.</td>
</tr>
<tr>
<td>lymphoma</td>
<td>Cancer that begins in the cells of the immune system.</td>
</tr>
<tr>
<td>maintenance dose</td>
<td>The amount of drug that is needed over the long-term to reach a stable, therapeutic response.</td>
</tr>
<tr>
<td>malignant</td>
<td>Cancerous. Malignant tumors, or cancer, have the ability to invade adjacent tissues and spread throughout the body. Thus, malignant tumors can become life threatening.</td>
</tr>
<tr>
<td>mammogram</td>
<td>An X-ray picture of the breast. The x-ray images make it possible to detect tumors that cannot be felt. They can also find microcalcifications that may signal the presence of cancer.</td>
</tr>
<tr>
<td>maraviroc</td>
<td>The generic name of Selzentry, a drug used to treat HIV infection that only works in people whose HIV uses a specific receptor (CCR5) to infect the cell.</td>
</tr>
<tr>
<td>maternal serum screening test</td>
<td>A blood test that looks at the levels of certain substances in a pregnant woman's blood. These tests are used to find the risk for having certain birth defects. They can't tell for sure whether a pregnancy has a birth defect.</td>
</tr>
<tr>
<td>MCH</td>
<td>An abbreviation for &quot;mean corpuscular hemoglobin&quot;. The average amount of hemoglobin in the average red blood cell. The normal range for the MCH is 27 - 32 picograms. MCH is a standard part of a CBC (complete blood count) test.</td>
</tr>
<tr>
<td>MCV</td>
<td>An abbreviation for &quot;mean corpuscular volume&quot;. The average size of a red blood cell. The normal range for the MCV is 80 - 100 femtoliters. MCV is a standard part of the CBC (complete blood count) test.</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>Someone whose ancestors come from one of the countries bordering the Mediterranean Sea. These countries include but are not limited to: Spain, southern France, Italy, and Greece.</td>
</tr>
<tr>
<td>metabolic syndrome</td>
<td>Also called &quot;insulin resistance&quot;. A combination of factors (like abnormal cholesterol, abdominal obesity, high blood sugar, and high blood pressure) that increases the risk of getting both heart disease and diabetes.</td>
</tr>
<tr>
<td>metabolism or metabolize</td>
<td>The way drugs and other substances are broken down for use in the body and elimination.</td>
</tr>
<tr>
<td>metastasis</td>
<td>The spread of cancer from one part of the body to another.</td>
</tr>
<tr>
<td>methylation</td>
<td>A process by which a methyl group is added to the DNA base cytosine. This process often decreases the amount of gene product that is made. For example, tumor suppressor genes are often methylated which decrease their function and lead to cancer.</td>
</tr>
<tr>
<td>mlh1</td>
<td>A mismatch repair (MMR) gene located on chromosome 3. Mutations in MLH1 are associated with Lynch syndrome (also called HNPCC) and greatly increase the chance of cancer -- especially colon.</td>
</tr>
<tr>
<td>MMR gene</td>
<td>Mismatch repair gene, a gene that functions as a part of the “spell check” system of a cell. Mutations in MMR genes are involved in causing some hereditary cancer syndromes.</td>
</tr>
<tr>
<td>morbidity</td>
<td>A diseased state.</td>
</tr>
<tr>
<td>MSH2</td>
<td>A mismatch repair (MMR) gene located on chromosome 2. Mutations in MLH1 are associated with Lynch syndrome (also called HNPCC) and greatly increase the chance of cancer -- especially colon.</td>
</tr>
<tr>
<td>multifactorial inheritance</td>
<td>Conditions that are caused by an interaction between more than one gene and environmental (non-genetic) factors. Most common human diseases seem to be multifactorial, including diabetes, heart disease, mental illness, and most birth defects. A family history of a multifactorial condition usually increases the risk for other relatives.</td>
</tr>
<tr>
<td>multiple myeloma</td>
<td>Cancer that begins in the cells of the immune system.</td>
</tr>
<tr>
<td>multisite</td>
<td>Multisite Testing looks for the three BRCA gene mutations that cause 80% to 90% of all hereditary breast and ovarian cancers in Ashkenazi Jewish people. This test gives you a clear result: either you have one of these three mutations, or you don’t. If you don’t, it is possible to have a different BRCA mutation that was not tested for.</td>
</tr>
<tr>
<td>mutation</td>
<td>A change in the DNA code that may cause a gene not to function in the normal way.</td>
</tr>
<tr>
<td>newborn screening</td>
<td>Testing that is done routinely after birth, to look for serious developmental, genetic and metabolic disorders. This testing is done so that important medical treatments or other actions can start before symptoms develop.</td>
</tr>
<tr>
<td>niacin</td>
<td>Also called &quot;nicotinic acid&quot;. Part of vitamin B3 found in foods like meat, fish, milk, eggs, green vegetables, and grains. Niacin supplements increase HDL, lower Lp(a), and to a lesser degree, lower LDL cholesterol. Common brand names include: Niacor, Niaspan, Nicolar, Nicotinex Elixir, and Slo-Niacin.</td>
</tr>
<tr>
<td>non-invasive procedure</td>
<td>Procedures that do not require insertion of an instrument or device through the skin or a bodily orifice for diagnosis or treatment.</td>
</tr>
<tr>
<td>Term</td>
<td>Description</td>
</tr>
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</tr>
<tr>
<td>Noonan syndrome</td>
<td>A genetic disorder that causes abnormal development of many parts of the body. It can be caused by a defect in one of four different genes (KRAS, PTPN11, RAF1, SOS1). Noonan syndrome may be inherited from a parent who has the condition, or may happen by chance in a pregnancy.</td>
</tr>
<tr>
<td>obesity</td>
<td>Having a high amount of body fat. Usually defined by a body mass index (BMI) of 30 or higher.</td>
</tr>
<tr>
<td>omega 3-fatty acid</td>
<td>Also called &quot;fish oil&quot;. Omega-3 fatty acids from eating oily fish or taking fish oil supplements may lower triglycerides, slow the buildup of plaque in the arteries, and raise HDL (&quot;good&quot;) cholesterol. Too much omega-3 fatty acid is dangerous, so you should always talk to your doctor before starting supplements.</td>
</tr>
<tr>
<td>organs</td>
<td>A grouping of tissue that works together to perform a common function. Examples of organs include: stomach, lungs, and liver.</td>
</tr>
<tr>
<td>osteoma</td>
<td>Benign, bony tumors often on the skull or mandible (sometimes a clinical finding with FAP patients).</td>
</tr>
<tr>
<td>over-the-counter</td>
<td>OTC or over-the-counter drugs can be bought without a prescription. OTC drugs still carry certain risks and may interact with other drugs.</td>
</tr>
<tr>
<td>P-53</td>
<td>A gene which normally regulates the cell cycle and protects the cell from damage to its genome. Mutations in this gene cause cells to develop cancer.</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>Short for &quot;pregnancy-associated plasma protein A&quot;, a substance found in pregnant women's blood. Low levels of PAPP-A at 8-14 weeks of pregnancy have been associated with risk for Down syndrome and pregnancy complications.</td>
</tr>
<tr>
<td>pedigree</td>
<td>A diagram of biological relationships that usually includes information on each relative's medical history.</td>
</tr>
<tr>
<td>premenopausal</td>
<td>The time when a women is entering menopause until it is complete -- often defined as from the time periods become irregular until 12 months after the last period.</td>
</tr>
<tr>
<td>phenotype</td>
<td>Characteristics that can be seen or measured and are often the result of genes and environment working together. Examples include things like eye color, weight, IQ, cholesterol levels, or drug response.</td>
</tr>
<tr>
<td>phenotyping</td>
<td>Tests that measure specific traits or characteristics that can be caused by genes and/or environmental factors. This is in contrast to genotype testing that only looks at genetic information.</td>
</tr>
<tr>
<td>placebo</td>
<td>A phony treatment or &quot;sugar pill&quot;. Researchers often compare people taking a drug with those taking a placebo to better measure the real effects of the drug.</td>
</tr>
<tr>
<td>placenta</td>
<td>Also called the afterbirth, the placenta is the tissue that connects the developing baby to the mother's uterus. It develops as part of the pregnancy and has the same DNA as the developing baby. The placenta allows for the exchange of nutrients, waste and gases between the developing baby and the mother.</td>
</tr>
<tr>
<td>plaque</td>
<td>Related to heart disease, plaque is the buildup of cholesterol, calcium, and other substances on the inside walls of the arteries causing the arteries to be more narrow and less flexible.</td>
</tr>
<tr>
<td>plasma</td>
<td>The liquid part of the blood that carries blood cells and other components.</td>
</tr>
<tr>
<td>polymorphism</td>
<td>Natural differences in a DNA sequence that are usually common and do not cause disease.</td>
</tr>
<tr>
<td>polyp</td>
<td>A usually non-cancerous growth or tumor protruding from the lining of an organ, such as the colon. Left untreated, polyps have an increased risk of becoming cancerous.</td>
</tr>
<tr>
<td>poor metabolizer</td>
<td>Produce inactive drug metabolism enzyme or no enzyme at all. Poor metabolizers may have a reduced response or no response and may have increased side effects.</td>
</tr>
<tr>
<td>poor metabolizer</td>
<td>Poor metabolizers have a pair of drug metabolism genes that don't work properly. They make very little or none of the enzyme coded for by that pair of genes. This causes slower metabolism or the inability to process certain drugs. People have many drug metabolism genes and can be different kinds of metabolizers for each.</td>
</tr>
<tr>
<td>postmenopausal</td>
<td>The time in a woman's life after menopause is complete -- often defined as starting 12 months after the last period.</td>
</tr>
<tr>
<td>pre-cancerous</td>
<td>Condition of the tissue, such as a polyp, that can turn into a cancer if not treated or removed.</td>
</tr>
<tr>
<td>preconception</td>
<td>Generally considered the period of time when a person is planning pregnancy but has not yet conceived (become pregnant).</td>
</tr>
<tr>
<td>pre-diabetes</td>
<td>Diagnosed when glucose (sugar) levels are higher than normal, but not high enough to make the diagnosis of diabetes -- usually a fasting glucose of 100 to 125 mg/dl or a glucose of 140 to 199 mg/dl after glucose tolerance test.</td>
</tr>
<tr>
<td>predisposition</td>
<td>Any condition, genetic or other, that renders an individual more susceptible to disease.</td>
</tr>
<tr>
<td>preimplantation</td>
<td>A technique used with in vitro fertilization to test early-stage embryos for disease-causing genes, so that embryos without the disease-causing genes can be implanted in the mother's uterus.</td>
</tr>
<tr>
<td><strong>prenatal diagnosis</strong></td>
<td>Testing for diseases in the fetus or embryo before it is born.</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>presymptomatic</strong></td>
<td>The stage prior to an individual presenting with symptoms that are clinically relevant to the disease in question.</td>
</tr>
<tr>
<td><strong>prophylactic bilateral mastectomy</strong></td>
<td>A risk-reducing treatment where both breasts, as well as some of the surrounding tissue, are surgically removed in order to keep cancerous cells from forming.</td>
</tr>
<tr>
<td><strong>prophylactic bilateral oophorectomy</strong></td>
<td>A risk-reducing treatment where ovaries are surgically removed in order to keep cancerous cells from forming; recommended after childbearing is complete.</td>
</tr>
<tr>
<td><strong>protein</strong></td>
<td>Large, complex molecules made of amino acids that form body structures, enzymes, hormones, and antibodies. Proteins are all made based on the instructions in our genes. The amino acids we need to make new proteins are consumed in the protein we eat or made by the body.</td>
</tr>
<tr>
<td><strong>protein(s)</strong></td>
<td>The molecules that form the body, allow it to grow, and regulate how it works. Our bodies make the proteins we need using the instructions from our genes.</td>
</tr>
<tr>
<td><strong>receptor</strong></td>
<td>A protein on the surface of a cell that only binds with certain other molecules. When this happens, a cellular process can occur.</td>
</tr>
<tr>
<td><strong>rectum</strong></td>
<td>The last portion of the digestive tract, at the end of the colon.</td>
</tr>
<tr>
<td><strong>red blood cells</strong></td>
<td>A cell in the blood that carries oxygen to all parts of the body. Also called an erythrocyte.</td>
</tr>
<tr>
<td><strong>risk factor</strong></td>
<td>Anything that increases the chance of developing a certain disease or having a child with a specific condition. Risk factors might include your family history, lifestyle, other health conditions, blood test results, age, gender, and countless other factors.</td>
</tr>
<tr>
<td><strong>sarcoma</strong></td>
<td>A cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissues.</td>
</tr>
<tr>
<td><strong>screening</strong></td>
<td>In medicine, screening generally refers to a test or exam that is reasonably simple, inexpensive, and harmless that can be given to a large group of people in order to find a smaller group with a higher-than-average chance for a certain condition. These people will sometimes have more specific testing or be treated early before symptoms appear.</td>
</tr>
<tr>
<td><strong>selective estrogen receptor modulator</strong></td>
<td>Selective Estrogen Receptor Modulator (SERM) is a hormone-like drug that affects multiple tissues by interacting with receptors for the hormone estrogen. A particular SERM may have estrogen-like effects in some tissues and anti-estrogen effects in others.</td>
</tr>
<tr>
<td><strong>Selzentry</strong></td>
<td>The brand name of maraviroc, a drug used to treat HIV infection that only works in people whose HIV uses a specific receptor (CCR5) to enter the cell.</td>
</tr>
<tr>
<td><strong>sequencing</strong></td>
<td>A lab method that looks at each DNA nucleotide (A,T,G, and C) in a piece of DNA for differences (mutations) from the usual DNA sequence. A more labor intensive and expensive test that is often used when the specific mutations that cause a disease aren't known.</td>
</tr>
<tr>
<td><strong>serum CA-125</strong></td>
<td>A blood test used in an effort to detect ovarian cancer.</td>
</tr>
<tr>
<td><strong>serum ferritin</strong></td>
<td>A protein your body makes when it stores iron.</td>
</tr>
<tr>
<td><strong>siblings</strong></td>
<td>Brothers and/or sisters.</td>
</tr>
<tr>
<td><strong>sickle cell disease</strong></td>
<td>An inherited disorder in which the red blood cells have an abnormal crescent shape that affects blood flow. This disorder causes anemia because the abnormal blood cells don't survive long.</td>
</tr>
<tr>
<td><strong>sickle/beta-thalassemia</strong></td>
<td>A disease that occurs when someone inherits a sickle-cell anemia gene mutation from one parent and a beta-thalassemia gene mutation from the other parent. Symptoms are usually very similar to sickle cell disease.</td>
</tr>
<tr>
<td><strong>side effect</strong></td>
<td>An unintended and usually undesired reaction to a drug or treatment.</td>
</tr>
<tr>
<td><strong>Single Site</strong></td>
<td>Single Site Testing looks for just one BRCA mutation. This test can only be done for people who know the DNA sequence of a BRCA mutation that is running in their family. This test gives you a clear result: Either you have the mutation that was tested for or you don’t.</td>
</tr>
<tr>
<td><strong>southeast Asian</strong></td>
<td>Someone whose ancestors come from one of the countries south of China and east of India. These countries include but are not limited to: Vietnam, Cambodia, Laos, Burma, or Indonesia.</td>
</tr>
<tr>
<td><strong>spleen</strong></td>
<td>An organ in the abdomen that supports the immune system, destroys and filters out old blood cells, and holds a reserve of blood cells. People can live without a spleen.</td>
</tr>
<tr>
<td><strong>sporadic</strong></td>
<td>In reference to cancer, this means a cancer not caused by hereditary genetic mutations. Most cancers are sporadic.</td>
</tr>
<tr>
<td><strong>statin</strong></td>
<td>A group of drugs that lower the amount of cholesterol made naturally by the liver. When diet and exercise changes aren’t enough, statins are often the first choice for drug therapy. Commonly prescribed statins include: Lovastatin (Mevacor, Altoprev), Pravastatin (Pravachol), Simvastatin (Zocor), Fluvastatin (Lescol), Atorvastatin (Lipitor), and Rosuvastatin (Crestor).</td>
</tr>
<tr>
<td><strong>Stevens-Johnson syndrome</strong></td>
<td>An allergic reaction to a drug or infection that causes flu-like symptoms, skin wounds, and may affect other organs like the eyes and mouth.</td>
</tr>
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</tr>
<tr>
<td><strong>stroke</strong></td>
<td>Caused by a sudden lack of blood supply and oxygen to the brain. Usually happens because either a blood clot blocks a blood vessel in the brain (ischemic stroke) or a blood vessel breaks and bleeds into the brain (hemorrhagic stroke).</td>
</tr>
<tr>
<td><strong>symptom</strong></td>
<td>Any sign that a person has a condition or disease. Symptoms, like headache, fever, fatigue, nausea, vomiting, and pain, may not be specific but together point to an underlying cause.</td>
</tr>
<tr>
<td><strong>symptoms</strong></td>
<td>Changes or signs that are caused by or accompany a disease or condition. Symptoms are the evidence of that underlying disease or condition. Symptoms can be used to help diagnose a problem.</td>
</tr>
<tr>
<td><strong>tamoxifen</strong></td>
<td>A drug commonly used to treat patients with breast cancer, certain other cancers, and those at high risk for breast cancer. It works by interfering with the activity of the hormone estrogen, which feeds the growth of many, but not all breast cancers.</td>
</tr>
<tr>
<td><strong>toxic epidermal necrolysis</strong></td>
<td>A life-threatening allergic reaction started by certain drugs, infections, illnesses, and unknown factors. TEN can cause large areas of the skin to peel away, flu-like symptoms, and other complications. The condition gets worse quickly and usually requires hospitalization.</td>
</tr>
<tr>
<td><strong>transferrin saturation</strong></td>
<td>The percentage of transferrin (a protein that carries iron in the blood) that is currently carrying iron.</td>
</tr>
<tr>
<td><strong>translocation</strong></td>
<td>A genetic condition where material from one chromosome breaks off and sticks to another chromosome, or switches places with a part of another chromosome. There are different types of translocations, and they can have different effects on health and development.</td>
</tr>
<tr>
<td><strong>transvaginal ultrasound</strong></td>
<td>A type of ultrasound done by inserting an ultrasound probe into the vagina. This allows a view of a woman's reproductive organs, including the uterus, ovaries, cervix, and vagina.</td>
</tr>
<tr>
<td><strong>triglycerides</strong></td>
<td>A type of energy-rich fat. High triglycerides (over 200mg/dL) increase the risk for heart disease and stroke.</td>
</tr>
<tr>
<td><strong>tropism</strong></td>
<td>The specific cell types that a virus can recognize and infect.</td>
</tr>
<tr>
<td><strong>tumor</strong></td>
<td>An abnormal mass of tissue that results from excessive cell division. Tumors may be benign (not cancerous) or malignant (cancerous).</td>
</tr>
<tr>
<td><strong>Turner syndrome</strong></td>
<td>A genetic condition in which a girl or woman does not have the usual pair of two X chromosomes. Instead, some or all of her cells are missing an X chromosome, or part of an X chromosome. Symptoms are variable but usually include short stature and infertility.</td>
</tr>
<tr>
<td><strong>ultra metabolizer</strong></td>
<td>Have more than two functional copies of a drug metabolism gene, and produce a larger-than-normal amount of enzyme. Ultra metabolizers may have a reduced or no response and may have increased side effects.</td>
</tr>
<tr>
<td><strong>ultrarapid metabolizer</strong></td>
<td>Ultrarapid metabolizers have extra copies of a gene involved in drug metabolism, so they make more enzyme than the average person. This results in faster metabolism of drugs processed by that enzyme.</td>
</tr>
<tr>
<td><strong>umbilical cord</strong></td>
<td>The cord that connects the developing baby to the placenta, which is attached to the mother’s uterus. The umbilical cord carries oxygen- and nutrient-rich blood to the developing baby.</td>
</tr>
<tr>
<td><strong>unconjugated estriol</strong></td>
<td>One of the three main estrogens produced by the body. Low levels of this substance are associated with risk for certain birth defects, including Down syndrome and trisomy 18. Also abbreviated “uE3.”</td>
</tr>
<tr>
<td><strong>variant</strong></td>
<td>Gene variations contribute to diversity and make people unique. When a certain form of a gene is seen in at least 1% of people, but not most people, it is called a variant. Variants may also increase or decrease a person’s risk for certain genetic diseases but usually don’t cause the disease themselves.</td>
</tr>
<tr>
<td><strong>vein</strong></td>
<td>Blood vessels that carry blood low in oxygen back to the heart.</td>
</tr>
<tr>
<td><strong>virtual colonoscopy</strong></td>
<td>A method of examining the colon by taking a series of X-rays (called a CT scan) and using a high-powered computer to reconstruct 2-D and 3-D pictures of the interior surfaces of the colon from these X-rays.</td>
</tr>
<tr>
<td><strong>VKORC1</strong></td>
<td>A gene that tells the body how to make vitamin K epoxide reductase (VKOR), an enzyme important in forming blood-clotting factors. A common VKORC1 gene variant (-1639G&gt;A) puts people at increased risk for complications when taking warfarin at standard doses.</td>
</tr>
<tr>
<td><strong>VLDL</strong></td>
<td>Very low density lipoprotein -- a type of “bad” cholesterol. High VLDL increases the risk for plaque buildup in the arteries and heart disease.</td>
</tr>
<tr>
<td><strong>VLDL3</strong></td>
<td>A subtype of VLDL [a “bad” cholesterol]. High VLDL3 increases heart disease risk the most and is a risk factor even when total cholesterol levels are normal. Diet and exercise changes are very effective for lowering VLDL3.</td>
</tr>
<tr>
<td><strong>warfarin</strong></td>
<td>The most commonly prescribed drug for preventing harmful blood clots from forming or from growing larger. Belongs to a class of drugs called anticoagulants or &quot;blood thinners.&quot;</td>
</tr>
<tr>
<td><strong>white blood cells</strong></td>
<td>A cell found in the blood whose primary job is to defend the body against infection.</td>
</tr>
<tr>
<td><strong>xanthoma</strong></td>
<td>Fat buildup that looks like a yellow lump under the skin, most commonly on the heels, hands, elbows, other joints, feet, and buttocks. Especially common in people with inherited high cholesterol like familial hypercholesterolemia.'</td>
</tr>
</tbody>
</table>
Administrative Policies
Unlisted Molecular Pathology CPT Code 81479

<table>
<thead>
<tr>
<th>Procedure covered by this policy:</th>
<th>Procedure Code(s)</th>
<th>Requires:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unlisted molecular pathology procedure</td>
<td>81479</td>
<td>Prior-authorization</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Claims Review and/or Payment Rules Apply</td>
<td>Sometimes</td>
</tr>
</tbody>
</table>

* - Clinical Review necessary prior to authorization for this procedure.
† - Additional information may be required upon claim receipt.

Click here for applicable Medicare NCD/LCD information

Description

This document outlines prior authorization and payment policies related to the unlisted molecular pathology CPT code 81479. This code is intended to be used for any molecular pathology test that is not specifically addressed by a Tier 1 or Tier 2 Molecular Pathology CPT or other assigned test-specific CPT code. The expectation is that labs will not self-assign Tier 1 or 2 codes for billing based upon their own interpretation of required effort.

The Centers for Medicare and Medicaid Services (CMS) establishes and publishes, in the Federal Register, relative value units (RVU's) for most CPT codes. RVU's are a weighted score used to determine the fee scales for procedures and services performed by professional providers. These RVU's may be used to determine allowances for reimbursement. Most lab codes have allowances published in the Clinical Lab Fee Schedule. However, for unlisted codes with no specific definition CMS may not assign RVU's or publish an allowance in the Clinical Lab Fee Schedule. Because CPT code 81479 will be used for a wide range of molecular tests, the billed amount is expected to vary greatly.

CPT code 81479 should ONLY be utilized when the performed test is a molecular pathology study not adequately described by a Tier 1 (81161-81383), Tier 2 (81400–81408), or other molecular pathology CPT code. Refer to the AMA CPT code long descriptors for a current, comprehensive listing of tests assigned a Tier 1 or Tier 2 CPT code.

Criteria

Prior Authorization Requirements for Unlisted Molecular Pathology Procedure 81479

When 81479 is the most appropriate procedure code, testing will be subject to prior authorization in the following circumstances:

- CPT code 81479 will be billed with any other Molecular Pathology CPT code from range 81161-81408 on the same date of service, OR
- CPT code 81479 is associated with a test (one or more CPT codes) that will be billed at an amount greater than or equal to $1000.00 for a single date of service.

When a claim meets the above requirements for prior authorization, the following information must be submitted for review:

- Laboratory that will be performing the test
• Details about the test being performed (test name, description, and available evidence supporting clinical validity and utility)
• All CPT codes that will be billed related to the test and intended fee
• The laboratory’s suggestion for the Tier 2 Molecular Pathology CPT code(s) that most closely approximates the required effort to perform the test
• Test indication for member
• Any applicable signs and symptoms or other reasons for testing
• Any applicable test results (laboratory, imaging, pathology, etc.)
• Any applicable family history
• How test results will impact patient care

Claims Review and/or Payment Rules for 81479

• All claims received that include CPT code 81479 are subject to review.
• CPT code 81479 must only be billed for a unique procedure that is not adequately addressed by any other CPT code. It cannot be used as an adjunct to other CPT codes to reflect increased test methodology complexity.
• Any claim meeting the following conditions will always undergo retrospective clinical review for medical necessity determination:
  o No prior authorization on file for 81479 in combination with the billing laboratory, AND
  o CPT code 81479 is billed in any of the following ways:
    ▪ CPT code 81479 is billed with any other Molecular Pathology CPT code from range 81161-81408 on the same date of service, OR
    ▪ CPT code 81479 is associated with a test billed at an amount greater than or equal to $1000.00 for a single date of service.
  o When a claim meets the above requirements, a retrospective clinical review will be initiated. The following information must be submitted for review:
    ▪ Laboratory that performed the test (if not the billing laboratory)
    ▪ Details about the test performed (test name, description/unique identifier, and available evidence supporting clinical validity and utility)
    ▪ The laboratory’s suggestion for the Tier 2 Molecular Pathology CPT code(s) that most closely approximates the required effort to perform the test
    ▪ Test indication for member
    ▪ Any applicable signs and symptoms or other reasons for testing
    ▪ Any applicable test results (laboratory, imaging, pathology, etc.)
    ▪ Any applicable family history
    ▪ How test results will impact patient care
• Reimbursement for CPT code 81479 will be handled in the following manner:
  o 81479 must be submitted with the laboratory’s suggestion for the Tier 2 Molecular Pathology CPT code(s) that most closely approximates the required effort to perform the test (regardless of whether clinical review is required).
  o This recommendation and the billed amount will be reviewed and compared with administratively established thresholds.
Charges will be processed if all of the following are met:

- All required information is provided
- The test meets medical necessity criteria if applicable
- The amount billed is consistent with the level of effort as determined both by the lab's assessment, as well as internal review and reimbursement thresholds

<table>
<thead>
<tr>
<th>NCD/LCD Jurisdiction and CPT Codes</th>
<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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References

2. CMS Clinical Lab Fee Schedule (CLFS)
### Molecular Pathology Tier 2 Molecular CPT Codes

<table>
<thead>
<tr>
<th>Procedures covered by this policy:</th>
<th>Requires:</th>
<th>Claims Review and/or Payment Rules Apply,†</th>
<th>Prior-authorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)</td>
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<td>Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)</td>
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<td></td>
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<tr>
<td>Molecular pathology procedure, Level 3 (eg, &gt;10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])</td>
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<td>Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)</td>
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<td>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)</td>
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<tr>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons)</td>
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<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
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<tr>
<td>Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of &gt;50 exons, sequence analysis of multiple genes on one platform)</td>
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<tr>
<td>Molecular pathology procedure, Level 9 (eg, analysis of &gt;50 exons in a single gene by DNA sequence analysis)</td>
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</tbody>
</table>

* - Clinical Review necessary prior to authorization for this procedure.
† - Additional information may be required upon claim receipt.

[Click here for applicable Medicare NCD/LCD information](#)
Description
This document outlines prior authorization and payment policies related to the "Tier 2 Molecular Pathology" CPT codes in range 81400-81408. Tier 2 codes are intended to report a wide range of molecular pathology procedures for which Tier 1, or test-specific, CPT codes have not been assigned. Tier 2 codes are organized and assigned based on level of technical and interpretive effort required.

Requests to have a specific test assigned to a Tier 2 CPT code are reviewed and implemented by the AMA. Additions are published a few times yearly and a current, comprehensive listing is available at: http://www.ama-assn.org/resources/doc/cpt/mopath-maaa-tier1-tier2.pdf. The expectation is that labs will not self-assign Tier 2 codes based upon their own interpretation of required effort. If the test has not been assigned to the appropriate Tier 2 CPT code, unlisted CPT code 81479 is to be used (see that policy if applicable).

Please note: This policy provides general guidance for any test that may be billed using CPT codes 81400-81408. However, this policy only applies when no test-specific policy exists. Please review the full list of policies to determine if a more appropriate policy is available.

Criteria
Prior Authorization Requirements

CPT codes 81400 through 81404

CPT codes 81400 through 81404 do NOT routinely require prior authorization.

Some tests billed using Tier 2 CPT codes 81400-81404 have test-specific policies in place. PLEASE NOTE that any available test-specific policy takes precedence over this general policy. Therefore, some tests billed with CPT codes 81400-81404 may require prior authorization based on those test-specific policies.

CPT codes 81405 through 81408

- CPT codes 81405 through 81408 ALWAYS require prior authorization. The following information must be submitted for review:
  - Details about the test being performed (test name, description, and/or unique identifier)
  - Laboratory that will be performing the test
  - All CPT codes that will be billed related to the test
  - Test indication for member
  - Any applicable signs and symptoms or other reasons for testing
  - Any applicable test results (laboratory, imaging, pathology, etc.)
  - Any applicable family history
  - How test results will impact patient care

- If prior authorization is not obtained, claims will be suspended. These codes will be identified upon claim submission and the above information must be provided for review or the claim will not be payable.
Claims Review and/or Payment Rules for 81400-81408

CPT codes 81400 through 81408

- All claims received for 81400 through 81408 are subject to review. CPT codes 81405 through 81408 are subject to prior authorization as described in Section 1-B above. However, any claim meeting the following conditions will always be reviewed:
  - No prior authorization on file for that CPT code combination and laboratory, AND
  - The CPT codes billed meet any of the following criteria:
    - At least one CPT code from range 81400-81408 billed on the same date of service with any other Molecular Pathology CPT code (range 81161-81479)
    - Any CPT code from range 81400-81408 billed with a multiplier (i.e., billed more than once on a single date of service).
    - Any CPT code from range 81400-81408 with a billed amount greater than or equal to $1000.00 (i.e., billed more than once on a single date of service).

- When a claim meets the above requirements, a retrospective clinical review will be initiated. The following information must be submitted for review:
  - Laboratory that performed the test (if not the billing laboratory)
  - Details about the test being performed (test name, description/unique identifier, and available evidence supporting clinical validity and utility)
  - All CPT codes that will be billed related to the test
  - Test indication for member
  - Any applicable signs and symptoms or other reasons for testing
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  - How test results will impact patient care

### NCD/LCD Jurisdiction and CPT Codes

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Specific Tests</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
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<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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No specific test/policy. Refer to MolDX.

#### CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV


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References

### Retired Molecular Pathology CPT Codes

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<th>Procedure Code(s)</th>
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<td>Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)</td>
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<td>Molecular diagnostics; enzymatic digestion, each enzyme treatment</td>
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<td>Molecular diagnostics; dot/slot blot production, each nucleic acid preparation</td>
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<td>Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation</td>
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<td>Nitrogen, Total; Urine, 24-hour Specimen</td>
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<td>Molecular diagnostics; nucleic acid probe, each</td>
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Molecular diagnostics; lysis of cells prior to nucleic acid extraction (eg, stool specimens, paraffin embedded tissue), each specimen | 83907 | Non-covered
Molecular diagnostics; amplification, signal, each nucleic acid sequence | 83908 | Non-covered
Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation | 83909 | Non-covered
Molecular diagnostics; interpretation and report | 83912 | Non-covered
Molecular diagnostics; RNA stabilization | 83913 | Non-covered
Mutation identification by enzymatic ligation or primer extension, single segment, each segment (eg, oligonucleotide ligation assay [OLA], single base chain extension [SBCE], or allele-specific primer extension [ASPE]) | 83914 | Non-covered

Description

CPT codes 83890-83914, commonly referred to as the molecular "stacking" codes because they could be combined to describe all the various steps of a molecular pathology procedure, have been retired as of 1/1/2013. These stacking codes were problematic because they provided only a basic description of the components or steps of a test, but these components are common to a wide variety of molecular tests performed for many reasons. Thus, they could not provide transparency into the specific test being performed.

The stacking codes have now been replaced by more test-specific CPT codes within the range 81161 to 81479, commonly called the MoPath Tier 1 and Tier 2 codes. Refer to the AMA CPT code long descriptors for a current, comprehensive listing of tests assigned a Tier 1 or Tier 2 CPT code. It is also possible that other CPT codes describing molecular testing procedures are applicable outside of the MoPath Tier 1/2 codes.

Criteria

Molecular Pathology Stacking Codes: 88390-83914

The molecular stacking CPT codes in range 88390 through 83914 have been retired and will therefore no longer be eligible for payment. If any CPT code in this range is submitted for reimbursement, the claim will be denied.

References

<table>
<thead>
<tr>
<th>Procedure covered by this policy:</th>
<th>Procedure Code(s)</th>
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<td>KRAS mutation analysis</td>
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<td>S3818</td>
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<tr>
<td>Complete gene sequence analysis; BRCA2 gene</td>
<td>S3819</td>
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<td>Complete BRCA1 and BRCA2 gene sequence analysis for susceptibility to breast and ovarian cancer</td>
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<td>Three-mutation BRCA1 and BRCA2 analysis for susceptibility to breast and ovarian cancer in Ashkenazi individuals</td>
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<td>Complete gene sequence analysis; MLH1 gene</td>
<td>S3828</td>
<td>Non-covered</td>
</tr>
<tr>
<td>Complete gene sequence analysis; MLH2 gene</td>
<td>S3829</td>
<td>Non-covered</td>
</tr>
<tr>
<td>Complete msh1 and msh2 gene sequence analysis for hereditary nonpolyposis colorectal cancer (HNPCC) genetic testing</td>
<td>S3830</td>
<td>Non-covered</td>
</tr>
<tr>
<td>Single-mutation analysis (in individual with a known MLH1 and MSH2 mutation in the family) for hereditary nonpolyposis colorectal cancer (HNPCC) genetic testing</td>
<td>S3831</td>
<td>Non-covered</td>
</tr>
<tr>
<td>Complete gene sequence analysis for cystic fibrosis genetic testing</td>
<td>S3835</td>
<td>Non-covered</td>
</tr>
<tr>
<td>Complete sequence analysis for hemochromotosis genetic testing</td>
<td>S3837</td>
<td>Non-covered</td>
</tr>
<tr>
<td>DNA analysis for f5 gene for susceptibility for Factor V Leiden thrombophilia</td>
<td>S3843</td>
<td>Non-covered</td>
</tr>
<tr>
<td>Genetic Testing for Tay-Sachs disease</td>
<td>S3847</td>
<td>Non-covered</td>
</tr>
<tr>
<td>Genetic Testing for Gaucher disease</td>
<td>S3848</td>
<td>Non-covered</td>
</tr>
<tr>
<td>Genetic Testing for Canavan disease</td>
<td>S3851</td>
<td>Non-covered</td>
</tr>
<tr>
<td>Genetic testing, comprehensive cardiac ion channel analysis, for variants in 5 major cardiac ion channel genes for individuals with high index of suspicion for familial long QT syndrome (LQTS) or related syndromes</td>
<td>S3860</td>
<td>Non-covered</td>
</tr>
<tr>
<td>Genetic testing, family-specific ion channel analysis, for blood-relatives of individuals (index case) who have previously tested positive for a genetic variant of a cardiac ion channel syndrome using either one of the above test configurations or confirmed results from another laboratory</td>
<td>S3862</td>
<td>Non-covered</td>
</tr>
</tbody>
</table>
Description
The Centers for Medicare & Medicaid Services (CMS) maintain level II Healthcare Common Procedure Coding System (HCPCS) codes designed primarily to describe procedures not adequately addressed by the American Medical Association's (AMA) CPT codes. Historically, several molecular and genomic tests that were previously only reportable through the use of non-specific molecular “stacking” CPT codes were assigned alphanumeric HCPCS codes in the S3000 range.

The AMA has now released Molecular Pathology Tier 1 and Tier 2 codes (81161-81479) that provide specificity around many molecular tests. Refer to the AMA CPT code long descriptors for a current, comprehensive listing of tests assigned a Tier 1 or Tier 2 CPT code. As a result, the S codes that applied to tests now adequately described by the AMA Molecular Pathology CPTs are no longer required and many have been retired by CMS in 2012.

Criteria
Retired S Codes
The HCPCS S codes in range S3711 through S3862 found to be redundant with newer test-specific Molecular Pathology CPT codes have been retired, and will therefore no longer be eligible for payment. If any CPT code in this range is submitted for reimbursement, the claim will be denied. The following table provides a crosswalk from the retired S codes to the now more appropriate CPT code(s).

<table>
<thead>
<tr>
<th>Retired S Code</th>
<th>Description</th>
<th>Applicable Code(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3711</td>
<td>Circulating tumor cell test</td>
<td>86152, 86153</td>
</tr>
<tr>
<td>S3713</td>
<td>KRAS mutation analysis</td>
<td>81275</td>
</tr>
<tr>
<td>S3818</td>
<td>Complete gene sequence analysis; BRCA1 gene</td>
<td>81214</td>
</tr>
<tr>
<td>S3819</td>
<td>Complete gene sequence analysis; BRCA2 gene</td>
<td>81216</td>
</tr>
<tr>
<td>S3820</td>
<td>Complete BRCA1 and BRCA2 gene sequence analysis for susceptibility to breast and ovarian cancer</td>
<td>81211</td>
</tr>
<tr>
<td>S3822</td>
<td>Single mutation analysis (in individual with a known BRCA1 or BRCA2 mutation in the family) for susceptibility to breast and ovarian cancer</td>
<td>81215</td>
</tr>
<tr>
<td>S3823</td>
<td>Three-mutation BRCA1 and BRCA2 analysis for susceptibility to breast and ovarian cancer in Ashkenazi individuals</td>
<td>81212</td>
</tr>
<tr>
<td>S3828</td>
<td>Complete gene sequence analysis; MLH1 gene</td>
<td>81292</td>
</tr>
<tr>
<td>S3829</td>
<td>Complete gene sequence analysis; MLH2 gene</td>
<td>81295</td>
</tr>
<tr>
<td>S3830</td>
<td>Complete MLH1 and MSH2 gene sequence analysis for hereditary nonpolyposis colorectal cancer (HNPCC) genetic testing</td>
<td>81292, 81295</td>
</tr>
<tr>
<td>S3831</td>
<td>Single-mutation analysis (in individual with a known MLH1 and MSH2 mutation in the family) for hereditary nonpolyposis colorectal cancer (HNPCC) genetic testing</td>
<td>81293, 81296</td>
</tr>
<tr>
<td>S3835</td>
<td>Complete gene sequence analysis for cystic fibrosis genetic testing</td>
<td>81222</td>
</tr>
</tbody>
</table>
### Retired S Codes

<table>
<thead>
<tr>
<th>Retired S Code</th>
<th>Description</th>
<th>Applicable Code(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3837</td>
<td>Complete sequence analysis for hemochromotosis genetic testing</td>
<td>81256, 81479</td>
</tr>
<tr>
<td>S3843</td>
<td>DNA analysis for f5 gene for susceptibility for Factor V Leiden thrombophilia</td>
<td>81241</td>
</tr>
<tr>
<td>S3847</td>
<td>Genetic Testing for Tay-Sachs disease</td>
<td>81255</td>
</tr>
<tr>
<td>S3848</td>
<td>Genetic Testing for Gaucher disease</td>
<td>81251</td>
</tr>
<tr>
<td>S3851</td>
<td>Genetic Testing for Canavan disease</td>
<td>81200</td>
</tr>
<tr>
<td>S3860</td>
<td>Genetic testing, comprehensive cardiac ion channel analysis, for variants in 5 major cardiac ion channel genes for individuals with high index of suspicion for familial long qt syndrome (lqts) or related syndromes</td>
<td>81280</td>
</tr>
<tr>
<td>S3862</td>
<td>Genetic testing, family-specific ion channel analysis, for blood-relatives of individuals (index case) who have previously tested positive for a genetic variant of a cardiac ion channel syndrome using either one of the above test configurations or confirmed results from another laboratory</td>
<td>81281</td>
</tr>
</tbody>
</table>

### Non-retired S Codes

There remain HCPCS S codes for molecular tests that have not been adequately replaced by Molecular Pathology CPT codes. These S codes remain in effect and may be used for billing purposes. Please refer to test-specific coverage policies for guidance. The following list includes examples of S codes that remain in effect. It is not intended to be comprehensive and serves as guidance only.

<table>
<thead>
<tr>
<th>Example S Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3721</td>
<td>Prostate cancer antigen 3 (PCA3) testing</td>
</tr>
<tr>
<td>S3722</td>
<td>Dose optimization by area under the curve (AUC) analysis, for infusional 5-fluorouracil</td>
</tr>
<tr>
<td>S3800</td>
<td>Genetic testing for amyotrophic lateral sclerosis (als)</td>
</tr>
<tr>
<td>S3833</td>
<td>Complete apc gene sequence analysis for susceptibility to familial adenomatous polyposis (fap) and attenuated fap</td>
</tr>
<tr>
<td>S3834</td>
<td>Single-mutation analysis (in individual with a known apc mutation in the family) for susceptibility to familial adenomatous polyposis (fap) and attenuated fap</td>
</tr>
<tr>
<td>S3840</td>
<td>Dna analysis for germline mutations of the ret proto-oncogene for susceptibility to multiple endocrine neoplasia type 2</td>
</tr>
<tr>
<td>S3841</td>
<td>Genetic testing for retinoblastoma</td>
</tr>
<tr>
<td>S3842</td>
<td>Genetic testing for von hippel-lindau disease</td>
</tr>
<tr>
<td>S3844</td>
<td>Dna analysis of the connexin 26 gene (gjb2) for susceptibility to congenital, profound deafness</td>
</tr>
<tr>
<td>S3845</td>
<td>Genetic testing for alpha-thalasemia</td>
</tr>
<tr>
<td>S3846</td>
<td>Genetic testing for hemoglobin E beta-thalasemia</td>
</tr>
<tr>
<td>S3849</td>
<td>Genetic Testing for Niemann-Pick disease</td>
</tr>
<tr>
<td>S3850</td>
<td>Genetic testing for sickle cell anemia</td>
</tr>
<tr>
<td>Example S Codes</td>
<td>Description</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
</tr>
<tr>
<td>S3852</td>
<td>Dna analysis for apoe epsilon 4 allele for susceptibility to alzheimer's disease</td>
</tr>
<tr>
<td>S3853</td>
<td>Genetic testing for myotonic muscular dystrophy</td>
</tr>
<tr>
<td>S3854</td>
<td>Gene expression profiling panel for use in the management of breast cancer treatment</td>
</tr>
<tr>
<td>S3855</td>
<td>Genetic testing for detection of mutations in the presenilin - 1 gene</td>
</tr>
<tr>
<td>S3861</td>
<td>Genetic testing, sodium channel, voltage-gated, type v, alpha subunit (scn5a) and variants for suspected brugada syndrome</td>
</tr>
<tr>
<td>S3865</td>
<td>Comprehensive gene sequence analysis for hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>S3866</td>
<td>Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (hcm) in an individual with a known hcm mutation in the family</td>
</tr>
<tr>
<td>S3870</td>
<td>CGH test developmental delay</td>
</tr>
<tr>
<td>S3890</td>
<td>Dna analysis, fecal, for colorectal cancer screening</td>
</tr>
</tbody>
</table>

References

Addendum: Medicare Policy

<table>
<thead>
<tr>
<th>Procedure(s) covered by this policy:</th>
<th>Procedure Code(s)</th>
<th>Requires:</th>
<th>Prior-authorization*</th>
<th>Lab Procedure Restrictions†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category I Molecular Pathology Tier 1 Codes</td>
<td>81161-81383</td>
<td>Sometimes. See Individual Policies</td>
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<tr>
<td>Category I Molecular Pathology Tier 2 Codes</td>
<td>81400-81408</td>
<td>Sometimes. See Individual Policies</td>
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<tr>
<td>Unlisted molecular pathology procedure</td>
<td>81479</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Multianalyte Assays with Algorithmic Analyses (MAAA)</td>
<td>0001M-0005M, 81500-81599</td>
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<td></td>
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<tr>
<td>Unlisted chemistry procedure</td>
<td>84999</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Criteria

For Medicare members, CareCore National (CCN) will use the following strategy for application of medical necessity criteria for coverage determinations:

- Apply test specific criteria from National Coverage Determination (NCD). If not available, then
- Apply test specific criteria from Local Coverage Determination (LCD) or third party test specific criteria (such as MolDx) referenced in LCD. As per CMS guidelines, billing lab’s state jurisdiction will apply. If not available, then
- Apply CCN test-specific criteria. If not available, then
- Apply CCN clinical use policies.

Medicare policy information and associated links are located within each of CCN's test-specific policies when available.

For those tests where some form of Medicare policy is available but there is no corresponding CCN test-specific policy, the following table may be used to locate the applicable Medicare policy and associated links that will be used for medical necessity reviews.

<table>
<thead>
<tr>
<th>Test, Jurisdiction, Policy</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE (angiotensin converting enzyme) (eg, hereditary blood pressure regulation), insertion/deletion variant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>See LCD jurisdictions that refer to MolDX.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| LCD: MolDX (http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse^By^Topic|||)
<p>| 81400 MOPATH PROCEDURE LEVEL 1 | No | No | N/A |
| ATP7B (ATPase, Cu++ transporting, beta polypeptide) (eg, Wilson disease), full gene sequence |
| See LCD jurisdictions that refer to MolDX. |</p>
<table>
<thead>
<tr>
<th>Test, Jurisdiction, Policy</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?*</th>
</tr>
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<tbody>
<tr>
<td><strong>MOPATH PROEDURE LEVEL 7</strong></td>
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<td>No</td>
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**Avise PG Assay**

CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV


<table>
<thead>
<tr>
<th>Test</th>
<th>Jurisdiction</th>
<th>Diagnostics Required?</th>
<th>ICD9 Codes Required?</th>
<th>MolDX Referenced?</th>
</tr>
</thead>
<tbody>
<tr>
<td>84999 CLINICAL CHEMISTRY TEST</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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</table>

VA, NC, SC, WV


<table>
<thead>
<tr>
<th>Test</th>
<th>Jurisdiction</th>
<th>Diagnostics Required?</th>
<th>ICD9 Codes Required?</th>
<th>MolDX Referenced?</th>
</tr>
</thead>
<tbody>
<tr>
<td>84999 CLINICAL CHEMISTRY TEST</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

See LCD jurisdictions that refer to MolDX.

LCD: MolDX ([http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx Website~MolDx~Browse By Topic~Covered Tests~8E3N6G3285?open&navmenu=Browse%5By%5ETopic%7C%7C%7C%7C%7C%7C](http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx Website~MolDx~Browse By Topic~Covered Tests~8E3N6G3285?open&navmenu=Browse%5By%5ETopic%7C%7C%7C%7C%7C%7C))

<table>
<thead>
<tr>
<th>Test</th>
<th>Jurisdiction</th>
<th>Diagnostics Required?</th>
<th>ICD9 Codes Required?</th>
<th>MolDX Referenced?</th>
</tr>
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<tbody>
<tr>
<td>84999 CLINICAL CHEMISTRY TEST</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
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</table>

**BCR/ABL Fusion Gene**

AR, LA, MS, CO, NM, OK, TX


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<thead>
<tr>
<th>Test</th>
<th>Jurisdiction</th>
<th>Diagnostics Required?</th>
<th>ICD9 Codes Required?</th>
<th>MolDX Referenced?</th>
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</thead>
<tbody>
<tr>
<td>81206 BCR/ABL1 GENE MAJOR BP</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>81207 BCR/ABL1 GENE MINOR BP</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>81208 BCR/ABL1 GENE OTHER BP</td>
<td>Yes</td>
<td>No</td>
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</table>

CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV

LCD: L33541 ([http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33541&ContrlId=283&ver=20&ContrlVer=2&SearchType=Advanced&CoverageSelection=Local&ArticleType=SAd%7cEd&PolicyType=Final&s=All&CnttrtType=1%7c8%7c9&CptHcpcsCode=81292&kq=true&bc=IAAAABAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33541&ContrlId=283&ver=20&ContrlVer=2&SearchType=Advanced&CoverageSelection=Local&ArticleType=SAd%7cEd&PolicyType=Final&s=All&CnttrtType=1%7c8%7c9&CptHcpcsCode=81292&kq=true&bc=IAAAABAAAAAAA%3d%3d&))

<table>
<thead>
<tr>
<th>Test</th>
<th>Jurisdiction</th>
<th>Diagnostics Required?</th>
<th>ICD9 Codes Required?</th>
<th>MolDX Referenced?</th>
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<tbody>
<tr>
<td>81206 BCR/ABL1 GENE MAJOR BP</td>
<td>No</td>
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<td>Yes</td>
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<tr>
<td>81207 BCR/ABL1 GENE MINOR BP</td>
<td>No</td>
<td>No</td>
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<tr>
<td>81208 BCR/ABL1 GENE OTHER BP</td>
<td>No</td>
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DE, DC, MD, NJ, PA


<table>
<thead>
<tr>
<th>Test</th>
<th>Jurisdiction</th>
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<th>ICD9 Codes Required?</th>
<th>MolDX Referenced?</th>
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<tbody>
<tr>
<td>81206 BCR/ABL1 GENE MAJOR BP</td>
<td>Yes</td>
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<tr>
<td>81207 BCR/ABL1 GENE MINOR BP</td>
<td>Yes</td>
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<td>No</td>
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</tr>
<tr>
<td>81208 BCR/ABL1 GENE OTHER BP</td>
<td>Yes</td>
<td>No</td>
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</table>

FL, PR, VI
<table>
<thead>
<tr>
<th>Test, Jurisdiction, Policy</th>
<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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</thead>
<tbody>
<tr>
<td>LCD: L33703 [1](<a href="http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33703&amp;ContrId=368&amp;ver=11&amp;ContrVer=1&amp;Date=&amp;DocID=L33703&amp;SearchType=Advanced&amp;bc=KAAAAAgAAAAAAA%3d%3d&amp;">http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33703&amp;ContrId=368&amp;ver=11&amp;ContrVer=1&amp;Date=&amp;DocID=L33703&amp;SearchType=Advanced&amp;bc=KAAAAAgAAAAAAA%3d%3d&amp;</a></td>
<td>81206 BCR/ABL1 GENE MAJOR BP</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>81207 BCR/ABL1 GENE MINOR BP</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>81208 BCR/ABL1 GENE OTHER BP</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>VA, NC, SC, WV</td>
<td>LCD: L33599 [2](<a href="http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33599&amp;ContrId=234&amp;ver=27&amp;ContrVer=1&amp;Date=&amp;DocID=L33599&amp;SearchType=Advanced&amp;bc=KAAAAAgAAAAAAA%3d%3d&amp;">http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33599&amp;ContrId=234&amp;ver=27&amp;ContrVer=1&amp;Date=&amp;DocID=L33599&amp;SearchType=Advanced&amp;bc=KAAAAAgAAAAAAA%3d%3d&amp;</a></td>
<td>81206 BCR/ABL1 GENE MAJOR BP</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>81207 BCR/ABL1 GENE MINOR BP</td>
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<td>No</td>
</tr>
<tr>
<td></td>
<td>81208 BCR/ABL1 GENE OTHER BP</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CAPN3 (Calpain 3) (eg, limb-girdle muscular dystrophy [LGMD] type 2A, calpainopathy), full gene sequence</td>
<td>See LCD jurisdictions that refer to MolDX. LCD: MolDX [3](<a href="http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDxWebsite~MolDx~BrowseByTopic~General~9BMLRK6738?open&amp;navmenu=BrowseByTopic">http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDxWebsite~MolDx~BrowseByTopic~General~9BMLRK6738?open&amp;navmenu=BrowseByTopic</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBFB/MYH11 (inv(16)) (eg, acute myeloid leukemia), qualitative, and quantitative, if performed</td>
<td>See LCD jurisdictions that refer to MolDX. LCD: MolDX [3](<a href="http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDxWebsite~MolDx~BrowseByTopic~General~9BMLRK6738?open&amp;navmenu=BrowseByTopic">http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDxWebsite~MolDx~BrowseByTopic~General~9BMLRK6738?open&amp;navmenu=BrowseByTopic</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCND1/IGH (BCL1/IgH, t(11;14)) (eg, mantle cell lymphoma) translocation analysis, major breakpoint, qualitative, and quantitative, if performed</td>
<td>See LCD jurisdictions that refer to MolDX. LCD: MolDX [3](<a href="http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDxWebsite~MolDx~BrowseByTopic~General~9BMLRK6738?open&amp;navmenu=BrowseByTopic">http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDxWebsite~MolDx~BrowseByTopic~General~9BMLRK6738?open&amp;navmenu=BrowseByTopic</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), full gene sequence</td>
<td>See LCD jurisdictions that refer to MolDX. LCD: MolDX [3](<a href="http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDxWebsite~MolDx~BrowseByTopic~General~9BMLRK6738?open&amp;navmenu=BrowseByTopic">http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDxWebsite~MolDx~BrowseByTopic~General~9BMLRK6738?open&amp;navmenu=BrowseByTopic</a></td>
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<td>CHD7 Gene Testing</td>
<td>See LCD jurisdictions that refer to MolDX. LCD: MolDX [3](<a href="http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDxWebsite~MolDx~BrowseByTopic~ExcludedTests~98ZTBQ4502?open&amp;navmenu=BrowseByTopic">http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDxWebsite~MolDx~BrowseByTopic~ExcludedTests~98ZTBQ4502?open&amp;navmenu=BrowseByTopic</a></td>
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Addendum: Medicare Policy

Test, Jurisdiction, Policy | Test-Specific Criteria? | Required ICD9 Codes? | Refer to MolDX?*
---|---|---|---
81479 UNLISTED MOLECULAR PATHOLOGY | No | No | N/A

Chemosensitivity and Chemoresistance Assays: DiSC Assay (Differential staining cytotoxicity assay); ATP (Adenosine Triphosphate) Assay; MTT (Methyl Thiazolyl Tetrazolium) Assay; HDRA® (AntiCancer Inc) Assay; EVA-PCD™ (Rational Therapeutics) Assay; Oncotech EDR® (Exiqon Diagnostics)

CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV
84999 CLINICAL CHEMISTRY TEST | Yes | No | No

VA, NC, SC, WV
84999 CLINICAL CHEMISTRY TEST | Yes | No | No

Chimerism

CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV
LCD: L33541 (http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33541&ContrId=364&ContrVer=1&Date=&DocID=L33541&SearchType=Advanced&bc=KAAAAAgAAAAAAA%3d%3d&)
81267 CHIMERISM ANAL NO CELL SELECT | No | No | Yes
81268 CHIMERISM ANAL W/CELL SELECT | No | No | Yes

FL, PR, VI
81267 CHIMERISM ANAL NO CELL SELECT | No | No | No
81268 CHIMERISM ANAL W/CELL SELECT | No | No | No

VA, NC, SC, WV
81267 CHIMERISM ANAL NO CELL SELECT | No | No | Yes
81268 CHIMERISM ANAL W/CELL SELECT | No | No | Yes

See LCD jurisdictions that refer to MolDX.

LCD: MolDX (http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Covered%20Tests~9BN732628?open&navmenu=Browse%5EBy%5ETopic%7C%7C%7C%7C)
81267 CHIMERISM ANAL NO CELL SELECT | Yes | No | N/A
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<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?*</th>
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<td>81268 CHIMERISM ANAL W/CELL SELECT</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
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</table>

**E2A/PBX1 (t(1;19))** (eg, acute lymphocytic leukemia), translocation analysis, qualitative, and quantitative, if performed

See LCD jurisdictions that refer to MolDX.

LCD: MolDX

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse*By*Topic|113x590|)

| 81401 MOPATH PROCEDURE LEVEL 2 | No | No | N/A |

**EML4/ALK (inv(2))** (eg, non-small cell lung cancer), translocation or inversion analysis

See LCD jurisdictions that refer to MolDX.

LCD: MolDX

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse*By*Topic|113x590|)

| 81401 MOPATH PROCEDURE LEVEL 2 | No | No | N/A |

**ENG and ACVRL1 Gene Testing (HHT Type 1 and Type 2)**

See LCD jurisdictions that refer to MolDX.

LCD: MolDX

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse*By*Topic|113x590|)

| 81479 UNLISTED MOLECULAR PATHOLOGY | No | No | N/A |
| 81403 MOPATH PROCEDURE LEVEL 4 | No | No | N/A |

**ETV6/RUNX1 (t(12;21))** (eg, acute lymphocytic leukemia), translocation analysis, qualitative, and quantitative, if performed

See LCD jurisdictions that refer to MolDX.

LCD: MolDX

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse*By*Topic|113x590|)

| 81401 MOPATH PROCEDURE LEVEL 2 | No | No | N/A |

**EWSR1/ERG (t(21;22))** (eg, Ewing sarcoma/peripheral neuroectodermal tumor), translocation analysis, qualitative, and quantitative, if performed

See LCD jurisdictions that refer to MolDX.

LCD: MolDX

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse*By*Topic|113x590|)

| 81401 MOPATH PROCEDURE LEVEL 2 | No | No | N/A |

**EWSR1/FLI1 (t(11;22))** (eg, Ewing sarcoma/peripheral neuroectodermal tumor), translocation analysis, qualitative, and quantitative, if performed

See LCD jurisdictions that refer to MolDX.

LCD: MolDX

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse*By*Topic|113x590|)

<p>| 81401 MOPATH PROCEDURE LEVEL 2 | No | No | N/A |</p>
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<th>Required ICD9 Codes?</th>
<th>Refer to MolDX?</th>
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<td>EWSRT1/WT1 ((11;22)) (eg, desmoplastic small round cell tumor), translocation analysis, qualitative, and quantitative, if performed</td>
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<td>81401 MOPATH PROCEDURE LEVEL 2</td>
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<td>F11 (coagulation factor XI) (eg, coagulation disorder), common variants (eg, E117X [Type II], F283L [Type III], IVS14del14, and IVS14+1G&gt;A [Type I])</td>
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<td>F13B (coagulation factor XIII, B polypeptide) (eg, hereditary hypercoagulability), V34L variant</td>
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<td>F7 (coagulation factor VII [serum prothrombin conversion accelerator]) (eg, hereditary hypercoagulability), R353Q variant</td>
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<td>81400 MOPATH PROCEDURE LEVEL 1</td>
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<td>F8 (coagulation factor VIII) (eg, hemophilia A), inversion analysis, intron 1 and intron 22A</td>
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<td>81403 MOPATH PROCEDURE LEVEL 4</td>
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<td>N/A</td>
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<td>FGB (fibrinogen beta chain) (eg, hereditary ischemic heart disease), -455G&gt;A variant</td>
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<td>81400 MOPATH PROCEDURE LEVEL 1</td>
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<td>FIP1L1/PDGFRα (del[4q12]) (eg, imatinib-sensitive chronic eosinophilic leukemia), qualitative, and quantitative, if performed</td>
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<td>Refer to MolDX?*</td>
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<td>FLT3 Gene Variants</td>
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<td>CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV</td>
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<td>See LCD jurisdictions that refer to MolDX.</td>
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<td>FOXO1/PAX3 (t(12;13)) (eg, Ewing sarcoma/peripheral neuroectodermal tumor), translocation analysis, qualitative, and quantitative, if performed</td>
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<td>GJB2/GJB6 Gene Testing</td>
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<td>Test, Jurisdiction, Policy</td>
<td>Test-Specific Criteria?</td>
<td>Required ICD9 Codes?</td>
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<td>81252 GJB2 GENE FULL SEQUENCE</td>
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<td>81253 GJB2 GENE KNOWN FAM VAR</td>
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<td>Human Platelet Antigen 1 genotyping (HPA-1), ITGB3 (integrin, beta 3 [platelet glycoprotein IIla], antigen CD61 [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), HPA-1a/b (L33P)</td>
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<td>Human Platelet Antigen 2 genotyping (HPA-2), GP1BA (glycoprotein lb [platelet], alpha polypeptide [GPIba]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), HPA-2a/b (T145M)</td>
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<td>Human Platelet Antigen 5 genotyping (HPA-5), ITGA2 (integrin, alpha 2 [CD49B, alpha 2 subunit of VLA-2 receptor] [GPIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), HPA-5a/b (K505E)</td>
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MLRK6738?open&navmenu=Browse*By*Topic][link]) | 81400 MOPATH PROCEDURE LEVEL 1 | No | No | N/A |

Human Platelet Antigen 6 genotyping (HPA-6w), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa, antigen CD61] [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), HPA-6a/b (R489Q)

| See LCD jurisdictions that refer to MolDX.  
LCD: MolDX  
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MLRK6738?open&navmenu=Browse*By*Topic][link]) | 81400 MOPATH PROCEDURE LEVEL 1 | No | No | N/A |

Human Platelet Antigen 9 genotyping (HPA-9w), ITGA2B (integrin, alpha 2b [platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41] [GPIIb]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), HPA-9a/b (V837M)

| See LCD jurisdictions that refer to MolDX.  
LCD: MolDX  
([http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9B
MLRK6738?open&navmenu=Browse*By*Topic][link]) | 81400 MOPATH PROCEDURE LEVEL 1 | No | No | N/A |

IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common exon 4 variants (eg, R132H, R132C)

| See LCD jurisdictions that refer to MolDX.  
LCD: MolDX  
([http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9B
MLRK6738?open&navmenu=Browse*By*Topic][link]) | 81403 MOPATH PROCEDURE LEVEL 4 | No | No | N/A |

IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common exon 4 variants (eg, R140W, R172M)

| See LCD jurisdictions that refer to MolDX.  
LCD: MolDX  
([http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9B
MLRK6738?open&navmenu=Browse*By*Topic][link]) | 81403 MOPATH PROCEDURE LEVEL 4 | No | No | N/A |

IGH/IGK Gene Rearrangement

| AR, LA, MS, CO, NM, OK, TX  
LCD: L34796 ([http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34796&ContrId=331&ver=45&ContrVer=1&DDate=&DocID=L34796&SearchType=Advanced&bc=KAAAAAgAAAAAAA%3d%3d&][link]) | 81261 IGH GENE REARRANGE AMP METH | Yes | No | No |

81263 IGH VARI REGIONAL MUTATION | Yes | No | No |

CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV  
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<td>81263 IGH VARI REGIONAL MUTATION PROBE</td>
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**DE, DC, MD, NJ, PA**


| 81261 IGH GENE REARRANGE AMP METH | Yes | No | No |
| 81263 IGH VARI REGIONAL MUTATION PROBE | Yes | No | No |

**FL, PR, VI**


| 81261 IGH GENE REARRANGE AMP METH | No | No | No |
| 81262 IGH GENE REARRANG DIR PROBE | No | No | No |
| 81263 IGH VARI REGIONAL MUTATION PROBE | No | No | No |
| 81264 IGK REARRANGEABN CLONAL POP | No | No | No |

**VA, NC, SC, WV**


| 81261 IGH GENE REARRANGE AMP METH | No | No | Yes |
| 81262 IGH GENE REARRANG DIR PROBE | No | No | Yes |
| 81263 IGH VARI REGIONAL MUTATION PROBE | No | No | Yes |
| 81264 IGK REARRANGEABN CLONAL POP | No | No | Yes |

See LCD jurisdictions that refer to MolDX.

LCD: MolDX ([http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse^By^Topic|]]

| 81261 IGH GENE REARRANGE AMP METH | No | No | N/A |
| 81262 IGH GENE REARRANG DIR PROBE | No | No | N/A |
| 81263 IGH VARI REGIONAL MUTATION PROBE | No | No | N/A |
| 81264 IGK REARRANGEABN CLONAL POP | No | No | N/A |

IGH@/BCL2 (t(14;18)) (eg, follicular lymphoma) translocation analysis; major breakpoint region (MBR) and minor cluster region (mcr) breakpoints, qualitative or quantitative

See LCD jurisdictions that refer to MolDX.
### Addendum: Medicare Policy

**Test, Jurisdiction, Policy**

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**JAK2 Variant Analysis**

**AR, LA, MS, CO, NM, OK, TX**

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**AZ, MT, ND, UT, WY, SD, ID, AK, WA, OR**

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**CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV**

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**DE, DC, MD, NJ, PA**

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**FL, PR, VI**

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**VA, NC, SC, WV**

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See LCD jurisdictions that refer to MolDX.

**JAK2 (Janus kinase 2) (eg, myeloproliferative disorder), exon 12 sequence and exon 13 sequence, if Performed**

**AZ, MT, ND, UT, WY, SD, ID, AK, WA, OR**

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<td>KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), common variants (eg, D816V, D816Y, D816F)</td>
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<td>MPL (myeloproliferative leukemia virus oncogene, thrombopoietin receptor, TPOR) (eg, myeloproliferative disorder), common variants (eg, W515A, W515K, W515L, W515R)</td>
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### Addendum: Medicare Policy

**Test, Jurisdiction, Policy**

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**myPAP DNA Test**

See LCD jurisdictions that refer to MolDX.

LCD: MolDX


84999 CLINICAL CHEMISTRY TEST

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**NPM1 Variant Analysis**

AR, LA, MS, CO, NM, OK, TX

LCD: L34796

(http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34796&ContrId=331&ver=45&ContrVer=1&Date=&DocID=L34796&SearchType=Advanced&bc=AAAAAgAAAAA%3d%3d&)

81310 NPM1 GENE

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CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV

LCD: L33541


81310 NPM1 GENE

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DE, DC, MD, NJ, PA

LCD: L34796

(http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34796&ContrId=319&ver=45&ContrVer=1&Date=&DocID=L34796&SearchType=Advanced&bc=AAAAAgAAAAA%3d%3d&)

81310 NPM1 GENE

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FL, PR, VI

LCD: L33703


81310 NPM1 GENE

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VA, NC, SC, WV

LCD: L33599

(http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33599&ContrId=234&ver=27&ContrVer=1&Date=&DocID=L33599&SearchType=Advanced&bc=AAAAAgAAAAA%3d%3d&)

81310 NPM1 GENE

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See LCD jurisdictions that refer to MolDX.

LCD: MolDX

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse*By*Topic|||)

81310 NPM1 GENE

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NPM1/ALK (t(2;5)) (eg, anaplastic large cell lymphoma), translocation analysis

See LCD jurisdictions that refer to MolDX.

LCD: MolDX

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse*By*Topic|||)

81401 MOPATH PROCEDURE LEVEL 2

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<tr>
<th>No</th>
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NRAS (neuroblastoma RAS viral oncogene homolog) (eg, colorectal carcinoma), exon 1 and exon 2 Sequences
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<th>Test-Specific Criteria?</th>
<th>Required ICD9 Codes?</th>
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<tr>
<td>81404 MOPATH PROCEDURE LEVEL 5</td>
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<td>NSD1 Gene Sequencing and Deletion/Duplication</td>
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<td>81479 UNLISTED MOLECULAR PATHOLOGY</td>
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<tr>
<td>PAX6 Gene Sequencing and Deletion/Duplication</td>
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<td>PAX8/PPARG (t(2;3) (q13;p25)) (eg, follicular thyroid carcinoma), translocation analysis</td>
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<td>81401 MOPATH PROCEDURE LEVEL 2</td>
<td>No</td>
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<td>PDGFRA (platelet-derived growth factor receptor alpha polypeptide) (eg, gastrointestinal stromal tumor), targeted sequence analysis (eg, exons 12, 18)</td>
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<td>PIK3CA Gene Testing</td>
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<td>PML/RARA Gene Rearrangement</td>
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### Test, Jurisdiction, Policy

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<tbody>
<tr>
<td>81315 PML/RARALPHA COM BREAKPOINTS</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>81316 PML/RARALPHA 1 BREAKPOINT</td>
<td>Yes</td>
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</table>

**CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV**


| 81315 PML/RARALPHA COM BREAKPOINTS | No | No | Yes |
| 81316 PML/RARALPHA 1 BREAKPOINT | No | No | Yes |

**DE, DC, MD, NJ, PA**


| 81315 PML/RARALPHA COM BREAKPOINTS | Yes | No | No |
| 81316 PML/RARALPHA 1 BREAKPOINT | Yes | No | No |

**FL, PR, VI**


| 81315 PML/RARALPHA COM BREAKPOINTS | No | No | No |
| 81316 PML/RARALPHA 1 BREAKPOINT | No | No | No |

**VA, NC, SC, WV**


| 81315 PML/RARALPHA COM BREAKPOINTS | No | No | Yes |
| 81316 PML/RARALPHA 1 BREAKPOINT | No | No | Yes |

**See LCD jurisdictions that refer to MolDX.**

**PreDx Diabetes Risk Score (DRS)**

**See LCD jurisdictions that refer to MolDX.**

**PTCH1 Gene Testing**

**See LCD jurisdictions that refer to MolDX.**

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Addendum: Medicare Policy
### Test, Jurisdiction, Policy

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**LCD: MolDX**

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Excluded%20Tests~98ZT271107?open&navmenu=Browse*By^Topic|||)  
81479 UNLISTED MOLECULAR PATHOLOGY  
No  
No  
N/A

**RET (ret proto-oncogene) (eg, Hirschsprung disease), full gene sequence**

See LCD jurisdictions that refer to MolDX.

**LCD: MolDX**

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse*By^Topic|||)  
81406 MOPATH PROCEDURE LEVEL 7  
No  
No  
N/A

**RPS19 Gene Testing**

See LCD jurisdictions that refer to MolDX.

**LCD: MolDX**

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Excluded%20Tests~98ZME31054?open&navmenu=Browse*By^Topic|||)  
81479 UNLISTED MOLECULAR PATHOLOGY  
No  
No  
N/A

**RUNX1/RUNX1T1 (t(8;21)) (eg, acute myeloid leukemia) translocation analysis, qualitative, and quantitative, if performed**

See LCD jurisdictions that refer to MolDX.

**LCD: MolDX**

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~9BMLRK6738?open&navmenu=Browse*By^Topic|||)  
81401 MOPATH PROCEDURE LEVEL 2  
No  
No  
N/A

**SEPT9 (Septin 9) (eg, colon cancer), methylation analysis**

See LCD jurisdictions that refer to MolDX.

**LCD: MolDX**

(http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Excluded%20Tests~937M7Q7863?open&navmenu=Browse*By^Topic|||)  
81401 MOPATH PROCEDURE LEVEL 2  
No  
No  
N/A

**Short Tandem Repeat (STR) Marker Testing**

**CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV**

**LCD: L33541**


81265 STR MARKERS SPECIMEN ANAL  
No  
No  
Yes

81266 STR MARKERS SPEC ANAL ADDL  
No  
No  
Yes

**FL, PR, VI**

**LCD: L33703**


81265 STR MARKERS SPECIMEN ANAL  
No  
No  
No

81266 STR MARKERS SPEC ANAL ADDL  
No  
No  
No

**VA, NC, SC, WV**
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<td>81265 STR MARKERS SPECIMEN ANAL</td>
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<td>81266 STR MARKERS SPEC ANAL ADDL</td>
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<td><strong>SULT4A1 Genotyping</strong></td>
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<td>81340 TRB@ GENE REARRANGE AMPLIFY</td>
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<td>81341 TRB@ GENE REARRANGE DIRPROBE</td>
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See LCD jurisdictions that refer to MolDX.


| 81479 UNLISTED MOLECULAR PATHOLOGY | No | No | N/A

See LCD jurisdictions that refer to MolDX.


| 81479 UNLISTED MOLECULAR PATHOLOGY | No | No | N/A

VEGFR2 Testing

See LCD jurisdictions that refer to MolDX.


| VWF (von Willebrand factor) (eg, von Willebrand disease type 2N), common variants (eg, T791M, R816W, R854Q) | No | No | N/A

See LCD jurisdictions that refer to MolDX.

<table>
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* The following jurisdictions have LCDs that refer to the MolDX site for additional test policy guidance for those CPT codes addressed in this policy.

**CA (NORTHERN), CA (SOUTHERN), AMERICAN SAMOA, GUAM, HAWAII, NORTHERN MARIANA ISLANDS, NV**

**VA, NC, SC, WV**

Addendum: Medicare Policy