2.04.91 General Approach to Genetic Testing

Original Policy Date: December 18, 2009
Effective Date: January 1, 2019
Section: 2.0 Medicine
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Policy Statement

Genetic testing classified in one of the categories below may be considered medically necessary when all of the criteria are met for each category, as outlined in the Rationale section:

1. Testing of an affected (symptomatic) individual’s germline DNA to benefit the individual (excluding reproductive testing)
   a. Diagnostic
   b. Prognostic
   c. Therapeutic
2. Testing cancer cells of an affected individual to benefit the individual
   a. Diagnostic
   b. Prognostic
   c. Therapeutic
3. Testing an asymptomatic individual to determine future risk of disease

Genetic testing that does not meet the criteria for a specific category is considered investigational or not medically necessary, according to the standard definitions used for these terms (see Policy Guidelines section).

Genetic testing is considered not medically necessary when any of the following situations exist:

- Testing is not considered standard of care, such as when the clinical diagnosis can be made without the use of a genetic test
- Testing is not clinically appropriate for the patient’s condition (e.g., when it would not change diagnosis and/or management). Other situations where testing is not clinically appropriate include, but are not limited to:
  - Testing performed entirely for nonmedical (e.g., social) reasons
  - Testing not expected to provide a definitive diagnosis that would obviate the need for further testing
- Testing is performed primarily for the convenience of the patient, physician, or other health care provider
- Testing would result in outcomes that are equivalent to outcomes using an alternative strategy, and the genetic test is more costly

Policy Guidelines

For the following category of testing, the benefit of testing is for a family member rather than the individual being tested. In this category, the criteria developed are for clinical utility.

- Testing of an affected individual’s germline to benefit family member(s)

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended
standard terminology “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

Table PG2. American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

General Information

Claims for molecular genetic testing should clearly identify the test type and the indications for testing. Appropriate HCPCS codes or CPT code modifiers should be utilized when available.

This policy applies only if there is not a separate Blue Shield Medical Policy that outlines specific criteria for testing. If a separate medical policy does exist, then the criteria for medical necessity in that policy supersede the guidelines in this policy.

This policy does not include cytogenetic testing (karyotyping), biochemical testing, or molecular testing for infectious disease.

This policy does not address prenatal testing.

The following Web sites may provide additional information on specific genetic tests and genetic testing laboratories:

- Agency for Healthcare Research and Quality: Genetic Testing  
- American College of Medical Genetics (ACMG): Translating Genes Into Health®  
  - https://www.acmg.net/
- Centers for Disease Control and Prevention: Public Health Genomics  
  - http://www.cdc.gov/genomics/default.htm
- Evaluation of Genomic Applications in Practice and Prevention (EGAPP)  
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2743609/
- Hayes, Inc.  
  - https://www.hayesinc.com/subscribers/displayLogin.do
- Mayo Clinic Mayo Medical Laboratories: Lab-Specific Test Indexes
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Coding

If the specific analyte is listed in codes 81200-81355 or 81400-81408, that CPT code would be reported. If the specific analyte is not listed in the more specific CPT codes, unlisted code 81479 would be reported.

Description

Commercially available genetic tests can guide intervention in symptomatic or asymptomatic people, identify people at risk for future disorders, predict the prognosis of diagnosed disease, and predict treatment response. This conceptual framework offers an outline for evaluating the utility of genetic tests by classifying the types of genetic tests into clinically relevant categories and developing criteria that can be used for evaluating tests in each category.

Related Policies

- Carrier Screening for Genetic Diseases
- General Approach to Evaluating the Utility of Genetic Panels
- Invasive Prenatal (Fetal) Diagnostic Testing
- Preimplantation Genetic Testing

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Most genetic tests are lab tests available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.
Rationale

Background
The purpose of this conceptual framework is to assist evaluation of the utility of genetic tests. In providing a framework for evaluating genetic tests, this review will not determine the clinical utility of genetic testing for specific disorders. Rather, it provides guidelines that can be applied to a wide range of tests.

This conceptual framework applies only if there is not a separate evidence review that outlines specific criteria for testing. If a separate review exists, then the criteria for medical necessity in that evidence review supersede the guidelines herein.

This conceptual framework does not include cytogenetic testing (karyotyping), biochemical testing, or molecular testing for infectious disease.

This conceptual framework also does not address reproductive genetic testing. There are separate evidence reviews for genetic testing in the reproductive setting, addressing, eg, carrier testing for genetic diseases is addressed in Blue Shield of California Medical Policy: Carrier Screening for Genetic Diseases, invasive prenatal (fetal) diagnostic testing is addressed in Blue Shield of California Medical Policy: Invasive Prenatal (Fetal) Diagnostic Testing, and preimplantation genetic testing is addressed in Blue Shield of California Medical Policy: Preimplantation Genetic Testing.

The following categories of genetic testing are addressed herein (see Appendix 1):

1. Testing of an affected (symptomatic) individual’s germline to benefit the individual
   a. Diagnostic
   b. Prognostic
   c. Therapeutic

2. Testing cancer cells of an affected individual to benefit the individual
   a. Diagnostic
   b. Prognostic
   c. Therapeutic

3. Testing an asymptomatic individual to determine future risk of disease

4. Testing of an affected individual’s germline to benefit family members.

BCBSA genetic testing category 5 (Reproductive testing) is not addressed herein.

Definitions
Genetic Testing
Genetic testing involves the analysis of chromosomes, DNA, RNA, genes, or gene products to detect inherited (germline) or noninherited (somatic) genetic variants related to disease or health.

Carrier Testing
A carrier of a genetic disorder has 1 abnormal allele for a disorder. When associated with an autosomal recessive or X-linked disorder, carriers of the causative variant are typically unaffected. When associated with an autosomal dominant disorder, the person has 1 normal copy of the gene and 1 mutated copy of the gene; such a person may be affected with the disorder, may be unaffected but at high risk of developing the disease later in life, or may remain unaffected because of the sex-limited nature of the disease.

Carrier testing may be offered to people: (a) who have family members with a genetic condition; (b) who have family members who are identified carriers; and (c) who are members of ethnic or racial groups known to have a higher carrier rate for a particular condition.
Germline Variants
Germline variants are present in the DNA of every cell of the body, from the moment of conception. They include cells in the gonads (testes or ova) and could, therefore, be passed on to offspring.

Somatic Variants
Somatic variations occur with the passage of time and are restricted to a specific cell or cells derived from it. If these variants are limited to cells that are not in the gonads, they will not be passed on to offspring.

Pharmacogenomics
Pharmacogenomics studies how a person’s genetic makeup affects his or her body’s response to drugs.

Literature Review
General Principles of Genetic Tests
A test should be cleared or approved by the U.S. Food and Drug Administration or performed in a Clinical Laboratory Improvement Amendments-certified laboratory.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The following rubric outlines the steps in assessing a medical test. The first step is to formulate the clinical context and purpose of the test. Then the evidence is reviewed to determine whether the test is technically reliable, clinically valid, and clinically useful. However, as noted below, technical reliability is outside the scope of evidence reviews.1,2

Types of Genetic Tests Addressed in this Conceptual Framework
1. Testing of an affected (symptomatic) individual’s germline to benefit the individual (excluding reproductive testing)
   a. Diagnostic: To confirm or exclude genetic or heritable variants in a symptomatic person. This refers to a molecular diagnosis supported by the presence of a known pathogenic variant. For genetic testing, a symptomatic person is defined as an individual with a clinical phenotype correlated with a known pathogenic variant.
   b. Prognostic: To determine or refine estimates of disease natural history or recurrence in patients already diagnosed with disease in order to predict natural disease course (e.g., aggressiveness, recurrence, risk of death). This type of testing may use gene expression of affected tissue to predict the course of disease (e.g., testing breast cancer tissue with Oncotype DX).
   c. Therapeutic: To determine that a particular therapeutic intervention is effective (or ineffective) for an individual. To determine the probability of favorable or adverse response to medications. To detect genetic variants that alter risk of treatment response, adverse events, drug metabolism, drug effectiveness, etc. (e.g., cytochrome P450 testing). To detect genetic variants that adversely affect response to exposures in the environment that are ordinarily tolerated (e.g., G6PD deficiency, genetic disorders of immune function, aminoacidopathies).

2. Testing cancer cells of an affected individual to benefit the individual
   a. Diagnostic: To determine the origin of a cancer or to determine a clinically relevant subgroup into which a cancer is classified.
   b. Prognostic: To determine the risk of progression, recurrence, or mortality for a cancer that is already diagnosed.
   c. Therapeutic: To determine the likelihood that a patient will respond to a targeted cancer therapy that is based on the presence or absence of a specific variant.
3. Testing an asymptomatic individual to determine future risk of disease. To detect genetic variants associated with disorders that appear after birth, usually later in life. Such testing is intended for individuals with a family history of a genetic disorder, but who themselves have no features of the disorder, at the time of testing, in order to determine their risk for developing the disorder.

4. Testing of an affected individual's germline to benefit family member(s). To focus and direct family testing of asymptomatic relatives, by testing an individual with known disease but in whom the presence or absence of a pathogenic variant has not been determined.

**Medical Necessity Criteria**

The criteria listed below for medical necessity represent minimum criteria that must be met in each category to conclude that a test is medically necessary. Alternative approaches to grouping these factors are presented in Appendix 2. The tables in Appendix 2 list all factors considered for clinical utility, and the figures in Appendix 2 group the factors into a branching logic schematic that facilitates a decision whether the test does or does not meet clinical utility.

Genetic testing is considered **medically necessary** for a genetic or heritable disorder when the following are met.

For ALL genetic testing, the condition being tested for must have either:
- Reduced life expectancy OR
- At least moderate-to-severe morbidity.³

For the specific categories of testing, the following criteria must also be met:

1. Testing of an affected (symptomatic) individual's germline to benefit the individual (excluding reproductive testing)
   a. **Diagnostic**
      i. An association between the marker and the disorder has been established AND
      ii. Symptoms of the disease are present AND
      iii. A definitive diagnosis cannot be made based on history, physical examination, pedigree analysis, and standard diagnostic studies/tests AND
      iv. The clinical utility of identifying the variant has been established (see Appendix 2):
         1) Leads to changes in clinical management of the condition that improve outcomes OR
         2) Eliminates the need for further clinical workup or invasive testing OR
         3) Leads to discontinuation of interventions that are unnecessary and/or ineffective
   
   b. **Prognostic**
      i. An association between the marker and the natural history of the disease has been established AND
      ii. Clinical utility of identifying the variant has been established (see Appendix 2):
         1) Provides incremental prognostic information above that of standard testing AND
         2) Reclassifies patients into clinically relevant prognostic categories for which there are different treatment strategies AND
         3) Reclassification leads to changes in management that improve outcomes
   
   c. **Therapeutic**
      i. Genetic testing identifies variants of a phenotype/metabolic state that relate to different pharmacokinetics, drug efficacy, or adverse drug reactions AND
      ii. Clinical utility of identifying the variant has been established (see Appendix 2):
         1) Leads to initiation of effective medication(s) OR
         2) Leads to discontinuation of medications that are ineffective or harmful OR
         3) Leads to clinical meaningful change in dosing of medication that is likely to improve outcomes

2. Testing cancer cells of an affected individual to benefit the individual
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a. Diagnostic
   i. Genetic testing can establish the cell origin of a cancer when the origin is uncertain following standard workup AND
   ii. Clinical utility of identifying the variant has been established (see Appendix 2): 
      1) Start effective treatment OR
      2) Discontinue ineffective or harmful treatment

b. Prognostic
   i. An association between the marker and the natural history of the disease has been established AND
   ii. Clinical utility of identifying the variant has been established (see Appendix 2): 
      1) Provides incremental prognostic information above that of standard testing AND
      2) Reclassifies patients into clinically relevant prognostic categories for which there are different treatment strategies AND
      3) Reclassification leads to changes in management that improve outcomes

c. Therapeutic
   i. Association between a variant and treatment response to a particular drug has been established AND
   ii. Clinical utility has been established (see Appendix 2): 
      1) The patient is a candidate for targeted drug therapy associated with a specific variant AND
      2) There is a clinically meaningful improvement in outcomes when targeted therapy is given for the condition

3. Testing of an asymptomatic individual to determine future risk of disease
   i. An association between the marker and future disorder has been established AND
   ii. Clinical utility has been established (see Appendix 2): 
      1) There is a presymptomatic phase for this disorder and interventions or surveillance are available AND
      2) Interventions in the presymptomatic phase are likely to improve outcomes:
         a. Prevent or delay onset of disease OR
         b. Detect disease at an earlier stage during which treatment is more effective OR
         c. Discontinuation of ineffective or unnecessary interventions

Clinical Utility Criteria
For the following category, focusing on the benefit of testing for another individual, the definition of medical necessity may not apply. When an individual is tested to benefit a family member, and there is no benefit for the individual being tested, eligibility for coverage depends on individual plan benefit language. Individual plans may differ whether benefit structure allows testing of an individual to benefit an unaffected family member.

For these reasons, the following criteria are considered for clinical utility of testing and not for medical necessity.

4. Testing of an affected individual’s germline to benefit family members
   i. An association between the genetic variant and clinical disease has been established AND
   ii. Family members are available who may be at risk for the disorder AND
   iii. The individual tested has a clinical diagnosis of the condition (or represents the family member who is most likely to harbor the pathogenic variant), but genetic testing has not been performed AND
   iv. There is a presymptomatic phase for the disorder in which interventions are available AND
   v. Interventions in the presymptomatic phase are likely to improve outcomes in one of the following ways:
General Approach to Genetic Testing

1) Prevent or delay onset of disease
2) Detect disease at an earlier stage during which treatment is more effective
3) Discontinuation of interventions that are ineffective or unneeded

Limitations of Genetic Testing
- The testing methods may not detect all variants that may occur in a gene
- Genetic testing may identify variants of uncertain significance
- Genetic testing may not necessarily determine the clinical outcome
- Different genes can cause the same disease (genetic heterogeneity)
- A variant in a gene may cause different phenotypes (phenotypic heterogeneity)
- Some disease-causing genes may not yet be identified
- Genetic testing is subject to laboratory error

SUMMARY OF EVIDENCE
This conceptual framework addresses genetic testing in nonreproductive settings. Genetic testing in reproductive settings is addressed separately in Blue Shield of California Medical Policies (e.g., Carrier Screening for Genetic Diseases, Invasive Prenatal (Fetal) Diagnostic Testing, Preimplantation Genetic Testing). For categories of genetic testing for which the benefit of testing is the individual, criteria for medical necessity apply. When the benefit of testing is not for the individual, but for a family member, medical necessity criteria may not apply, and the criteria are developed for clinical utility.

Supplemental Information
Practice Guidelines and Position Statements
No guidelines or statements were identified.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in November 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

Appendix

Appendix 1. Categorization of Types of Testing Addressed in Evidence Reviews

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td>1a. Diagnostic</td>
</tr>
<tr>
<td></td>
<td>1b. Prognostic</td>
</tr>
<tr>
<td></td>
<td>1c. Therapeutic</td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td>2a. Diagnostic</td>
</tr>
<tr>
<td></td>
<td>2b. Prognostic</td>
</tr>
<tr>
<td></td>
<td>2c. Therapeutic</td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td></td>
</tr>
<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td>5a. Carrier testing: preconception</td>
</tr>
<tr>
<td></td>
<td>5b. Carrier testing: prenatal</td>
</tr>
<tr>
<td></td>
<td>5c. In utero testing: aneuploidy</td>
</tr>
<tr>
<td></td>
<td>5d. In utero testing: variants</td>
</tr>
<tr>
<td></td>
<td>5e. In utero testing: other</td>
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<tr>
<td></td>
<td>5f. Preimplantation testing with in vitro fertilization</td>
</tr>
</tbody>
</table>
Appendix 2. Approach to Determining Clinical Utility for Genetic Testing

Direct Evidence
If direct evidence is available on the impact of testing on outcomes, this evidence takes precedence. Examples of direct evidence are:
- Trial comparing outcomes with and without use of the test versus
- Association study of genetic testing with outcomes

Indirect Evidence
When direct evidence is not available, indirect evidence should be evaluated. Indirect evidence addresses 1 or more components of a chain of evidence, but does not itself connect the intervention with the outcome.

An example of indirect evidence is the accuracy of the genetic test for diagnosing the clinical condition (i.e., clinical sensitivity and specificity). If improved accuracy leads to improved diagnosis of the disorder, and if more accurate diagnosis leads to management changes that improve outcomes, then clinical utility has been established.

Many disorders are rare, and high-quality evidence on the efficacy of treatment is often lacking. This is particularly true for aspects of management such as increased surveillance for complications, ancillary treatments (e.g., physical therapy, occupational therapy), and referrals to specialists. When evidence on outcomes is lacking, consideration may be given to whether these aspects of care are considered standard of care for that disorder, especially when they are part of guidelines by authoritative bodies.

A number of factors influence the strength of indirect evidence that is needed to determine whether health outcomes are improved. None by itself is determinative of whether genetic testing should be performed, but the factors may be important determinants of the potential clinical utility of testing. We enumerate below 4 factors, each with an accompanying table (see Appendix Tables 1-4).

1. Factors impacting the strength of indirect evidence for diagnostic testing (categories 1a, 2a)

   Disease Characteristics
   - Is life expectancy reduced with this disorder?
   - What is the level of physical and/or psychosocial morbidity (disability) associated with the disorder?
     o Severe morbidity/disability
     o Moderate morbidity/disability
     o Minor or no morbidity/disability

   Impact of Genetic Testing on Diagnosis
   - Can genetic testing confirm the suspected diagnosis?
   - Can the diagnosis be confirmed by alternative methods without genetic testing?
     o Disorder is defined by the presence of genetic variant
     o Genetic testing is one of several factors contributing to diagnosis
     o Unable to make diagnosis without genetic testing in some patients
   - Can genetic testing rule out the disorder?
   - Can genetic testing eliminate further clinical workup?
     o Is this a disorder for which a diagnosis can be difficult, and the patient may be subjected to long and complicated workups?

   Impact of Genetic Testing on Clinical Management
   - Does confirmation of diagnosis by genetic testing lead to improved outcomes?
     o Initiation of effective treatment
     o Discontinuation of ineffective treatment
• Does confirmation of diagnosis by genetic testing lead to initiation of other management changes with uncertain impact on outcomes (e.g., referrals to specialists and/or ancillary care, initiate screening)?
• Does confirmation of diagnosis by genetic testing lead to initiation of other management changes that are considered “standard of care” treatment for disorder?

**Impact on Health Outcomes**
• Is there a definite improvement in health outcomes with genetic testing? For example:
  o Diagnosis cannot be made without genetic testing, and confirmation of diagnosis leads to initiation of effective treatment
• Is there a possible, but not definite, improvement in health outcomes with genetic testing? For example:
  o Diagnosis cannot be made without genetic testing, and confirmation of diagnosis leads to management changes with uncertain impact on outcomes
• Are there significant barriers to research, such as rarity of the disorder?
• What is the impact of genetic testing on lifestyle factors?
  o Employment/occupational decision making
  o Leisure activities
  o Reproductive decision-maker

**Appendix Table 1. Factors Influencing the Strength of an Indirect Chain of Evidence on Clinical Utility: Categories 1a, 2a**

<table>
<thead>
<tr>
<th>Disorder Characteristics</th>
<th>Impact on Diagnosis</th>
<th>Impact on Management</th>
<th>Impact on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Shortened life expectancy</td>
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<td></td>
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<tr>
<td>Severe morbidity/disability</td>
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<tr>
<td>Moderate morbidity/disability</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Minor or no morbidity/disability</td>
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<td></td>
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<tr>
<td>Confirmation diagnosis confirmed by variant</td>
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<td></td>
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<tr>
<td>Confirmation diagnosis otherwise unable to make diagnosis</td>
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<tr>
<td>Rules out disorder</td>
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</tr>
<tr>
<td>Eliminates need for other clinical workup</td>
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<tr>
<td>Initiate effective treatment for disorder</td>
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<tr>
<td>Discontinue ineffective treatment for disorder</td>
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<td></td>
<td></td>
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<tr>
<td>Initiate other management changes</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Provide “standard of care” treatment for disorder</td>
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<tr>
<td>Change in management with improved health outcomes</td>
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<tr>
<td>Change in management with uncertain impact on outcomes</td>
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<tr>
<td>Barriers to research</td>
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<tr>
<td>Impact on lifestyle factors</td>
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</table>

**2. Factors impacting the strength of indirect evidence for assessing risk of future disease in asymptomatic individuals (category 3)**

**Disease Characteristics**
• Is life expectancy reduced with this disorder?
• What is the level of physical and/or psychosocial morbidity (disability) associated with the disorder?
  o Severe morbidity/disability
  o Moderate morbidity/disability
  o Minor or no morbidity/disability
• Is there a presymptomatic phase during which a clinical diagnosis cannot be made?

**Impact of Genetic Testing on Defining Risk of Disease**
• Can genetic testing determine the risk of subsequent disease in at least a substantial proportion of the population tested?
• Is there a known variant in the family?
• Is the penetrance of the genetic variant known?
Are there other factors that impact the clinical expression of disease?

Impact of Genetic Testing on Management
- Does confirmation of risk lead to interventions that are indicated for this condition in the presymptomatic phase?
  - Interventions that prevent or delay disease onset
  - Surveillance for manifestations or complications of disease
- Does confirmation of risk by a positive genetic testing result lead to the initiation of other management changes that may or may not lead to improved outcomes (e.g., referrals to specialists and/or ancillary care, initiate screening)?
- Does a negative test confirm a lack of risk for the disease, and does this lead to discontinuation of interventions (e.g., surveillance) that would otherwise be performed?
- Is it likely that knowledge of variant status will lead to alterations in reproductive decision making?

Impact on Health Outcomes
- Is there a definite improvement in health outcomes with genetic testing? For example:
  - Risk assessment cannot be made without genetic testing, and confirmation of risk leads to initiation of effective preventive interventions that delay onset of disease
- Is there a possible, but not definite, improvement in health outcomes with genetic testing? For example:
  - Risk assessment cannot be made without genetic testing, and confirmation of risk leads to management changes with uncertain impact on outcomes
- Are there significant barriers to research, such as rarity of the disorder?
- What is the impact of genetic testing on lifestyle factors?
  - Employment/occupational decision making
  - Leisure activities
  - Reproductive decision-maker

Appendix Table 2. Factors Influencing the Strength of Indirect Evidence for Risk Assessment Testing: Category 3

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease Characteristics</th>
<th>Impact on Defining Risk</th>
<th>Impact on Management</th>
<th>Impact on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortened life expectancy</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe morbidity/disability</td>
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<td></td>
</tr>
<tr>
<td>Moderate morbidity/disability</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Minor or no morbidity/disability</td>
<td></td>
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<tr>
<td>Has presymptomatic stage</td>
<td></td>
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<tr>
<td>Determines risk in substantial proportion of patients</td>
<td></td>
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<tr>
<td>Known mutation in family</td>
<td></td>
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</tr>
<tr>
<td>Penetration is well known</td>
<td></td>
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</tr>
<tr>
<td>Other factors impact clinical course</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiate effective interventions in presymptomatic phase</td>
<td></td>
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<tr>
<td>Other management changes with uncertain impact</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative test leads to discontinuation of interventions</td>
<td></td>
<td></td>
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<tr>
<td>Likely to impact reproducive decision making</td>
<td></td>
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<tr>
<td>Definite improved health outcomes data lacking</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Possible improved health outcomes data lacking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barriers to research lifestyle factors</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

3. Factors influencing the strength of indirect evidence for prognosis testing (categories 1b, 2b)

Disease Characteristics
- Is life expectancy reduced with this disorder?
- What is the level of physical and/or psychosocial morbidity (disability) associated with the disorder?
  - Severe morbidity/disability
Impact of Genetic Testing on Prognosis

- Does the genetic test have an association with prognosis of disease?
- Does genetic testing lead to an incremental improvement in prognosis above that which can be done by usual testing?
- Does the genetic testing allow classification of patients into clinically credible prognostic groups?
  - Have these prognostic groups been defined clinically a priori?

Impact of Genetic Testing on Management

- Are different prognostic groups associated with different treatment interventions?
  - Type of intervention
  - Timing of intervention
- Has treatment according to risk category been demonstrated to improve outcomes?
- Is treatment according to risk category considered standard of care for this disorder?

Impact on Health Outcomes

- Is there a definite improvement in health outcomes with genetic testing? For example:
  - Reclassification by prognosis leads to changes in management that is known to be effective for the condition
- Is there a possible, but not definite, improvement in health outcomes with genetic testing? For example:
  - Reclassification by prognosis leads to changes in management with uncertain impact on outcomes
- Are there significant barriers to research, such as rarity of the disorder?
- What is the impact of testing on lifestyle factors?
  - Employment/occupational decision making
  - Leisure activities
  - Reproductive decision-maker

Appendix Table 3. Factors Influencing the Strength of Indirect Evidence: Categories 1b, 2b

<table>
<thead>
<tr>
<th>Disorder Characteristics</th>
<th>Impact on Prognosis</th>
<th>Impact on Management</th>
<th>Impact on Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Shortened life expectancy</td>
<td></td>
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<tr>
<td>Severe morbidity/disability</td>
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<tr>
<td>Moderate morbidity/disability</td>
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<td></td>
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<tr>
<td>Minor or no morbidity/disability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variant associated with prognosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incremental improvement above clinical measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contributes to ability to make diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically credible prognostic groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prognostic groups have different treatment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Treatment by prognostic group improve outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment by prognostic group is standard of care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite improved health outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible impact on outcomes data lacking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barriers to research</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact on lifestyle factors</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

4. Factors influencing the strength of indirect evidence for genetic variants that alter response to treatment (categories 1c, 2c)

Disease Characteristics

- Is life expectancy reduced with this disorder?
- What is the level of physical and/or psychosocial morbidity (disability) associated with the disorder?
  - Severe morbidity/disability
2.04.91 General Approach to Genetic Testing

- Moderate morbidity/disability
- Minor or no morbidity/disability
- Is there effective pharmacologic therapy for this disorder?

**Impact of Genetic Testing on Assessing Response to Treatment**
- Can genetic testing define variants associated with different pharmacokinetics of drug metabolism?
- Are these changes in drug metabolism clinically important?
  - Variants have been associated with clinically significant differences in outcomes of treatment
- Are there genetic variants associated with increased risk for adverse effects?

**Impact of Genetic Testing on Pharmacologic Management**
- Does identification of genetic variants lead to changes in pharmacologic management?
  - Initiation of alternate agents
  - Discontinuation ineffective agents
  - Changes in dosing

**Impact on Health Outcomes**
- Is there a definite improvement in health outcomes with genetic testing? For example:
  - Identification of variants leads to initiation of medications known to be effective
- Is there a possible, but not definite, improvement in health outcomes with genetic testing? For example:
  - Identification of variants leads to change in pharmacologic management with uncertain impact on outcomes
- Are there significant barriers to research, such as rarity of the disorder?

**Appendix Table 4. Factors Influencing the Strength of Indirect Evidence: Genetic Variants That Alter Response to Treatment (Categories 1c, 2c)**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease Characteristics</th>
<th>Impact on Response to Treatment</th>
<th>Impact on Management</th>
<th>Impact on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortened life expectancy</td>
<td>Severe morbidity/disability</td>
<td>Define variants with different pharmacokinetics</td>
<td>Variants lead to differences in outcomes</td>
<td>Definite improved health outcomes</td>
</tr>
<tr>
<td>Severe morbidity/disability</td>
<td>Moderate morbidity/disability</td>
<td>Different pharmacokinetics are clinically important</td>
<td>Variants with increased risk for adverse effects</td>
<td>Possible impact outcomes data lacking</td>
</tr>
<tr>
<td>Moderate morbidity/disability</td>
<td>Minor morbidity/disability</td>
<td>Effective pharmacologic therapy</td>
<td>Initiation of alternate agents</td>
<td>Barriers to research</td>
</tr>
<tr>
<td>Minor or no morbidity/disability</td>
<td>Effective pharmacologic therapy</td>
<td></td>
<td>Changes in dosing</td>
<td></td>
</tr>
</tbody>
</table>
Appendix Figure 1. Diagnostic Testing Schematic of an Affected Individual’s Germline to Benefit the Individual (category 1a)

CU: clinical utility.
Appendix Figure 2. Prognostic Testing of an Affected Individual’s Germline to Benefit the Individual (category 1b)

1. Testing an affected individual’s germline to benefit the individual

1b. Prognostic

Does this disorder have reduced life expectancy?

Yes

Does this disorder have at least moderate or severe morbidity?

Yes

Does genetic testing provide incremental prognostic information above that provided by standard testing?

Yes

Does testing reclassify patients into clinically relevant prognostic categories for which there are different treatment strategies?

Yes

Does treatment according to the defined prognostic categories improve outcomes?

Yes

Meets CU Criteria

Uncertain impact on outcomes, but standard of care

Indeterminate, consider clinical vetting

No

Does not meet CU Criteria

CU: clinical utility.
Appendix Figure 3. Therapeutic Testing of an Affected Individual's Germline to Benefit the Individual (category 1c)

1. Testing an affected individual's germline to benefit the individual
   1c. Therapeutic

   Does this disorder have reduced life expectancy?
   - Yes
   - No

   Does this disorder have at least moderate or severe morbidity?
   - Yes
   - No

   Does genetic testing identify variants which have different drug sensitivities or pharmacokinetics?
   - Yes
   - No

   Are the differences in sensitivity or metabolism clinically important?
   - Yes
   - No

   Are there clinically credible management changes associated with identification of genetic variants?
   - Yes
   - No

   Discontinue ineffective drug
   - Meets CU Criteria

   Start effective drug
   - Meets CU Criteria

   Change dose of drug
   - Do these changes in drug dosage improve health outcome?
   - Yes
   - No

   Uncertain but standard of care
   - Indeterminate, consider clinical vetting
   - Does not meet CU Criteria

CU: clinical utility.
Appendix Figure 4. Diagnostic Testing of DNA Cells from Cancer Cells of an Affected Individual to Benefit the Individual (category 2a)

CU: clinical utility.
Appendix Figure 5. Prognostic Testing of DNA from Cancer Cells of an Affected Individual to Benefit the Individual (category 2b)

2. Testing of DNA from cancer cells of an affected individual to benefit the individual

2b. Prognostic

- Does this disorder have reduced life expectancy?
  - Yes
  - Does this disorder have at least moderate or severe morbidity?
    - Yes
    - Does genetic testing provide incremental prognostic information above that provided by standard testing?
      - Yes
      - Does testing reclassify patients into clinically relevant prognostic categories for which there are different treatment strategies?
        - Yes
        - Does treatment according to the defined prognostic categories improve outcomes?
          - Yes
          - Meets CU Criteria
          - No
          - Does not meet CU Criteria
        - No
        - Does not meet CU Criteria
    - No
    - Does not meet CU Criteria
  - No
  - Does not meet CU Criteria

CU: clinical utility.
Appendix Figure 6. Therapeutic Testing of Cancer Cells of an Affected Individual to Benefit the Individual (category 2c)

2. Testing of DNA from cancer cells of an affected individual to benefit the individual

2c. Predictive testing for treatment response

Does this disorder have reduced life expectancy?

Yes → Does not meet CU Criteria

No → Does this disorder have at least moderate or severe morbidity?

Yes → Does not meet CU Criteria

No → Can genetic testing identify markers associated with treatment response?

Yes → Does not meet CU Criteria

No → Are there targeted drugs aimed at the specific genetic markers?

Yes → Does not meet CU Criteria

No → Is there a clinically meaningful improvement in outcomes for targeted treatment?

Yes → Does testing “turn off” ineffective treatment

No → Does not meet CU Criteria

CU: clinical utility.
Appendix Figure 7. Testing an Asymptomatic Individual to Determine Future Risk of Disease (category 3)

3. Testing an asymptomatic individual to determine future risk of disease

Does this disorder have reduced life expectancy?

Yes

Does this disorder have at least moderate or severe morbidity?

Yes

Does not meet CU Criteria

No

Can testing identify genetic markers indicating future risk of disease?

Yes

Is penetrance for these markers known, and are other factors that affect clinical expression well understood?

Yes

Is there a presymptomatic phase for this disorder in which interventions are available?

Yes

Interventions that improve outcomes:
- Prevent/delay onset of disease
- Detect disease at earlier stage that has more effective treatment
- Discontinue surveillance or screening interventions

Meets CU Criteria

Interventions with uncertain impact on outcomes but are standard of care

Indeterminate, consider clinical vetting

Interventions that are unlikely to improve outcomes

Does not meet CU Criteria

No

Does not meet CU Criteria

CU: clinical utility.
Appendix Figure 8. Testing an Affected Individual’s Determine DNA to Benefit Family Members (category 4)

CU: clinical utility.

References

Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- Physician order for genetic test
- Name and description of genetic test
- Name of laboratory that performed the test
- Any available evidence supporting the clinical validity/utility of the specific test
- CPT codes billed for the particular genetic test
- History and physical and/or consultation notes including:
  - Reason for performing test
  - Signs/symptoms/test results related to reason for genetic testing
  - Family history if applicable
  - How test result will impact clinical decision making

Post Service

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0009U</td>
<td>Oncology (breast cancer), ERBB2 (HER2) copy number by FISH, tumor cells from formalin fixed paraffin embedded tissue isolated using image-based dielectrophoresis (DEP) sorting, reported as ERBB2 gene amplified or non-amplified</td>
</tr>
<tr>
<td></td>
<td>0013U</td>
<td>Oncology (solid organ neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, fresh or frozen tissue or cells, report of specific gene rearrangement(s)</td>
</tr>
<tr>
<td></td>
<td>0014U</td>
<td>Hematology (hematolymphoid neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood or bone marrow, report of specific gene rearrangement(s)</td>
</tr>
<tr>
<td></td>
<td>0015U</td>
<td>Drug metabolism (adverse drug reactions), DNA, 22 drug metabolism and transporter genes, real-time PCR, blood or buccal swab, genotype and metabolizer status for therapeutic decision support</td>
</tr>
<tr>
<td></td>
<td>0016U</td>
<td>Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation</td>
</tr>
<tr>
<td></td>
<td>0017U</td>
<td>Oncology (hematolymphoid neoplasia), JAK2 mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of JAK2 mutation not detected or detected</td>
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<tr>
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<td>81163</td>
<td>BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis <strong>(Code effective 1/1/2019)</strong></td>
</tr>
<tr>
<td>Type</td>
<td>Code</td>
<td>Description</td>
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<tr>
<td></td>
<td>81164</td>
<td>BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) <strong>(Code effective 1/1/2019)</strong></td>
</tr>
<tr>
<td></td>
<td>81165</td>
<td>BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis <strong>(Code effective 1/1/2019)</strong></td>
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<tr>
<td></td>
<td>81166</td>
<td>BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) <strong>(Code effective 1/1/2019)</strong></td>
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<td>81167</td>
<td>BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) <strong>(Code effective 1/1/2019)</strong></td>
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<td>81200</td>
<td>ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g., E285A, Y231X)</td>
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<tr>
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<td>81201</td>
<td>APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
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<tr>
<td></td>
<td>81202</td>
<td>APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
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<tr>
<td></td>
<td>81203</td>
<td>APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants</td>
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<tr>
<td></td>
<td>81205</td>
<td>BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (e.g., Maple syrup urine disease) gene analysis, common variants (e.g., R183P, G278S, E422X)</td>
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<td>81206</td>
<td>BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative</td>
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<tr>
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<td>81207</td>
<td>BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative</td>
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<td>81208</td>
<td>BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative</td>
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<td>81209</td>
<td>BLM (Bloom syndrome, RecQ helicase-like) (e.g., Bloom syndrome) gene analysis, 2281del6ins7 variant</td>
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<tr>
<td></td>
<td>81210</td>
<td>BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)</td>
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<td></td>
<td>81211</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb) <strong>(Deleted code effective 1/1/2019)</strong></td>
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<td>81212</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants</td>
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<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants <strong>(Deleted code effective 1/1/2019)</strong></td>
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<td>BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb) <strong>(Deleted code effective 1/1/2019)</strong></td>
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<td></td>
<td>81216</td>
<td>BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
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<td></td>
<td>81217</td>
<td>BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
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<tr>
<td></td>
<td>81220</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines)</td>
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<tr>
<td></td>
<td>81221</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; known familial variants</td>
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<tr>
<td></td>
<td>81222</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; duplication/deletion variants</td>
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<td>81223</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; full gene sequence</td>
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<td></td>
<td>81224</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; intron 8 poly-T analysis (e.g., male infertility)</td>
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<td>CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)</td>
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<td>CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)</td>
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<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (e.g., bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)</td>
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<tr>
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<td>81229</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
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<td>EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)</td>
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<td>F9 (coagulation factor IX) (e.g., hemophilia B), full gene sequence</td>
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<td>F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G&gt;A variant</td>
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<td>F5 (coagulation factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant</td>
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<td>FANCC (Fanconi anemia, complementation group C) (e.g., Fanconi anemia, type C) gene analysis, common variant (e.g., IVS4+4A&gt;T)</td>
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<td>FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles</td>
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<td>FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and methylation status)</td>
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<td>FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (i.e., exons 14, 15)</td>
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<td>FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (e.g., D835, I836)</td>
</tr>
<tr>
<td>Type</td>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
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<td>-------------</td>
</tr>
<tr>
<td>2.04.91 General Approach to Genetic Testing Page 25 of 29</td>
<td>81247</td>
<td>G6PD (glucose-6-phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; common variant(s) (e.g., A, A-)</td>
</tr>
<tr>
<td>81248</td>
<td>G6PD (glucose-6-phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; known familial variant(s)</td>
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<tr>
<td>81249</td>
<td>G6PD (glucose-6-phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; full gene sequence</td>
<td></td>
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<tr>
<td>81250</td>
<td>G6PC (glucose-6-phosphatase, catalytic subunit) (e.g., Glycogen storage disease, type 1a, von Gierke disease) gene analysis, common variants (e.g., R83C, Q347X)</td>
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<tr>
<td>81251</td>
<td>GBA (glucosidase, beta, acid) (e.g., Gaucher disease) gene analysis, common variants (e.g., N370S, 84GG, L444P, IVS2+1G&gt;A)</td>
<td></td>
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<tr>
<td>81252</td>
<td>GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; full gene sequence</td>
<td></td>
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<tr>
<td>81253</td>
<td>GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; known familial variants</td>
<td></td>
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<tr>
<td>81254</td>
<td>GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (e.g., nonsyndromic hearing loss) gene analysis, common variants (e.g., 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])</td>
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<tr>
<td>81255</td>
<td>HEXA (hexosaminidase A [alpha polypeptide]) (e.g., Tay-Sachs disease) gene analysis, common variants (e.g., 1278insTATC, 1421+1G&gt;C, G269S)</td>
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<tr>
<td>81256</td>
<td>HFE (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D)</td>
<td></td>
</tr>
<tr>
<td>81257</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha 3.7, alpha 4.2, alpha 20.5, Constant Spring)</td>
<td></td>
</tr>
<tr>
<td>81258</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant</td>
<td></td>
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<tr>
<td>81259</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence</td>
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<tr>
<td>81260</td>
<td>IKBAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (e.g., familial dysautonomia) gene analysis, common variants (e.g., 2507+6T&gt;C, R696P)</td>
<td></td>
</tr>
<tr>
<td>81261</td>
<td>IGH@ (Immunoglobulin heavy chain locus) (e.g., leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (e.g., polymerase chain reaction)</td>
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<tr>
<td>81262</td>
<td>IGH@ (Immunoglobulin heavy chain locus) (e.g., leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (e.g., Southern blot)</td>
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<tr>
<td>81263</td>
<td>IGK@ (Immunoglobulin kappa light chain locus) (e.g., leukemia and lymphoma, B-cell), variable region somatic mutation analysis</td>
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<tr>
<td>81264</td>
<td>IGK@ (Immunoglobulin kappa light chain locus) (e.g., leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)</td>
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</tbody>
</table>
| 81265 | Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (e.g., pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic
<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>recipient germline [e.g., buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells</td>
<td>81266</td>
<td>Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (e.g., additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>Chimerism (engraftment) analysis, post transplantation specimen (e.g., hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection</td>
<td>81267</td>
<td>Chimerism (engraftment) analysis, post transplantation specimen (e.g., hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection</td>
</tr>
<tr>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants</td>
<td>81269</td>
<td>JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant</td>
</tr>
<tr>
<td>KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)</td>
<td>81275</td>
<td>MGMT (0-6-methylguanine-DNA methyltransferase) (e.g., glioblastoma multiforme), methylation analysis</td>
</tr>
<tr>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
<td>81288</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>MCOLN1 (mucolipin 1) (e.g., Mucolipidosis, type IV) gene analysis, common variants (e.g., IVS3-2A&gt;G, del6.4kb)</td>
<td>81290</td>
<td>MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)</td>
</tr>
<tr>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
<td>81293</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<tr>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
<td>81294</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
<td>81295</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
<td>81296</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>Type</td>
<td>Code</td>
<td>Description</td>
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<td>81299</td>
<td><strong>MSH6</strong> (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<td>81300</td>
<td><strong>MSH6</strong> (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<td>81301</td>
<td>Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed</td>
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<tr>
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<td>81302</td>
<td><strong>MECP2</strong> (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; full sequence analysis</td>
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<td>81303</td>
<td><strong>MECP2</strong> (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; known familial variant</td>
</tr>
<tr>
<td></td>
<td>81304</td>
<td><strong>MECP2</strong> (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; duplication/deletion variants</td>
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<td></td>
<td>81310</td>
<td><strong>NPM1</strong> (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, exon 12 variants</td>
</tr>
<tr>
<td></td>
<td>81313</td>
<td><strong>PCA3/KLK3</strong> (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (e.g., prostate cancer)</td>
</tr>
<tr>
<td></td>
<td>81315</td>
<td><strong>PML/RARalpha</strong>, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (e.g., promyelocytic leukemia) translocation analysis; common breakpoints (e.g., intron 3 and intron 6), qualitative or quantitative</td>
</tr>
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<td></td>
<td>81316</td>
<td><strong>PML/RARalpha</strong>, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (e.g., promyelocytic leukemia) translocation analysis; single breakpoint (e.g., intron 3, intron 6 or exon 6), qualitative or quantitative</td>
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<tr>
<td></td>
<td>81317</td>
<td><strong>PMS2</strong> (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
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<td>81318</td>
<td><strong>PMS2</strong> (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<tr>
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<td>81319</td>
<td><strong>PMS2</strong> (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<tr>
<td></td>
<td>81321</td>
<td><strong>PTEN</strong> (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis</td>
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<tr>
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<td>81322</td>
<td><strong>PTEN</strong> (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant</td>
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<tr>
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<td>81323</td>
<td><strong>PTEN</strong> (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant</td>
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<td>81324</td>
<td><strong>PMP22</strong> (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis</td>
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<tr>
<td></td>
<td>81325</td>
<td><strong>PMP22</strong> (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis</td>
</tr>
</tbody>
</table>
## General Approach to Genetic Testing

### Type | Code | Description
--- | --- | ---
81326 | PMP22 (Peripheral Myelin Protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81330 | SMAD1 (Sphingomyelin phosphodiesterase 1, acid lysosomal) (e.g., Niemann-Pick disease, Type A) gene analysis, common variants (e.g., R496L, L302P, fsP330)
81331 | SNRPN/UBE3A (Small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (e.g., Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332 | SERPINA1 (Serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (e.g., alpha-1-antitrypsin deficiency), gene analysis, common variants (e.g., *S and *Z)
81340 | TRB@ (T cell antigen receptor, beta) (e.g., leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (e.g., polymerase chain reaction)
81341 | TRB@ (T cell antigen receptor, beta) (e.g., leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (e.g., Southern blot)
81342 | TRG@ (T cell antigen receptor, gamma) (e.g., leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81350 | UGT1A1 (UDP Glucuronosyltransferase 1 family, polypeptide A1) (e.g., irinotecan metabolism), gene analysis, common variants (e.g., *28, *36, *37)
81355 | VKORC1 (Vitamin K Epoxide Reductase Complex, Subunit 1) (e.g., warfarin metabolism), gene analysis, common variant(s) (e.g., -1639G>A, c.173+1000C>T)
81361 | HBB (Hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (e.g., HbS, HbC, HbE)
81362 | HBB (Hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
81363 | HBB (Hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)
81364 | HBB (Hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
81400 | Molecular Pathology Procedure Level 1
81401 | Molecular Pathology Procedure Level 2
81402 | Molecular Pathology Procedure Level 3
81403 | Molecular Pathology Procedure Level 4
81404 | Molecular Pathology Procedure Level 5
81405 | Molecular Pathology Procedure Level 6
81406 | Molecular Pathology Procedure Level 7
81407 | Molecular Pathology Procedure Level 8
81408 | Molecular Pathology Procedure Level 9
81479 | Unlisted molecular pathology procedure

### HCPCS
None

### ICD-10
None
Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/18/2009</td>
<td>New Policy Adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>01/25/2010</td>
<td>Coding Update</td>
<td>Administrative Update</td>
</tr>
<tr>
<td>09/27/2013</td>
<td>Policy revision with position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/31/2015</td>
<td>Coding Update</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2016</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>05/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2016</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>06/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>08/01/2017</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>02/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>01/01/2019</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use for treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.