General Approach to Genetic Testing

Policy Number: 2.04.91  Last Review: 4/2017
Origination: 2/2015  Next Review: 4/2018

Policy
Note: Genetic testing may be excluded in some contracts. Verify benefits prior to review for Medical Necessity.

When Policy Topic is covered
Genetic testing classified in one of the categories below may be considered **medically necessary** when all 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)
   - Diagnostic testing
   - Prognostic testing
   - Therapeutic

2. Testing of DNA from cancer cells of an affected individual to benefit the individual
   - Diagnostic
   - Prognostic
   - Therapeutic

3. Testing an asymptomatic individual to determine future risk of disease
**When Policy Topic is not covered**

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

**Considerations**

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 DNA to benefit family member(s)

Genetic testing is considered investigational when the BCBSA TEC criteria are not met, including when there is insufficient evidence to determine whether the technology improves health outcomes.

Genetic testing is considered not medically necessary when:

- 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, for example, when it would not change diagnosis and/or management. Other situations where testing is not clinically appropriate include, but are not limited to:
  - testing is performed entirely for nonmedical (eg, social) reasons
  - testing is 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.

Effective in 2013, 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 of Procedure or Service

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.

This conceptual framework addresses genetic testing in nonreproductive settings. Genetic testing in reproductive settings is addressed separately. 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.

Background

The purpose of this policy is to provide assistance in evaluating the utility of genetic tests. In providing a framework for evaluating genetic tests, this policy will not attempt to determine the clinical utility of genetic testing for specific disorders. Rather, it provides guidelines that can be applied to a wide range of different 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 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, invasive prenatal (fetal) diagnostic testing, and preimplantation genetic testing.
The following categories of genetic testing will be addressed in this policy:
1. Testing of an affected (symptomatic) individual’s germline DNA to benefit the individual
   a. Diagnostic
   b. Prognostic
   c. Therapeutic

2. Testing of DNA from cancer cells of an affected individual to benefit the individual
   a. Diagnostic
   b. Prognostic
   c. Testing to predict treatment response

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

4. Testing of an affected individual’s germline DNA to benefit family member(s)

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 mutation are typically unaffected. When associated with an autosomal dominant disorder, the person has 1 normal and 1 mutated copy of the gene and may be affected with the disorder, may be unaffected but at high risk of developing the disease later in life, or the carrier 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 Mutations**
Mutations that are present in the DNA of every cell of the body, present from the moment of conception. These include cells in the gonads (testes or ova) and could, therefore be passed on to offspring.

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

**Pharmacogenomics**
Study of how a person’s genetic makeup affects the body’s response to drugs.

**Rationale**
This conceptual framework was created in May 2013 and has been updated periodically. The most recent update covers the period through December 31, 2015.

**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.

The accuracy and indications for the test should be derived from peer-reviewed literature that focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (ie, how results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.1,2
Types of Genetic Tests Addressed in This Evidence Review

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 mutations in a symptomatic person. This refers to a molecular diagnosis supported by the presence of a known pathologic mutation. For genetic testing, a symptomatic person is defined as an individual with a clinical phenotype correlated with a known pathologic mutation.
   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 mutations 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 mutation.

3. Testing an asymptomatic individual to determine future risk of disease. To detect genetic mutations 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 pathologic mutation 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 of the marker with 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 mutation 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 of the marker with the natural history of the disease has been established AND
ii. Clinical utility of identifying the mutation 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 mutation 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
   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 mutation has been established (see Appendix 2):
         1) Start effective treatment OR
         2) Discontinue ineffective or harmful treatment

   b. Prognostic
      i. An association of the marker with the natural history of the disease has been established AND
      ii. Clinical utility of identifying the mutation 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 of a mutation with 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 mutation AND
2) There is a clinically meaningful improvement in outcomes when targeted therapy is given for the condition.

3. Testing an asymptomatic individual to determine future risk of disease
   i. An association of the marker with 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/surveillance are available AND
       2) Interventions in the presymptomatic phase are likely to improve outcomes:
           a. Prevent/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 of the genetic mutation with 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 mutation), 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:
   1) Prevent/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 mutations that may occur in a gene
- Genetic testing may identify variants of unknown clinical significance
- Genetic testing may not necessarily determine the clinical outcome
- Different genes can cause the same disease (genetic heterogeneity)
- A mutation 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.

References:

**Billing Coding/Physician Documentation Information**

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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>81200</td>
<td>ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)</td>
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<tr>
<td>81201</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
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<td>81202</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
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<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants</td>
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<tr>
<td>81205</td>
<td>BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide)</td>
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gene analysis, common variants (eg, R183P, G278S, E422X)

81206 BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative

81207 BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative

81208 BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative

81209 BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant

81210 BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)

81211 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (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)

81162 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis

81212 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants

81213 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants

81214 BRCA1 (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)

81215 BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant

81216 BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis

81217 BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene
analysis; known familial variant

81218  CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
81219  CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
81220  CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221  CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222  CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223  CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224  CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
81228  Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
81229  Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
81161  DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
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<th>Code</th>
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<td>81235</td>
<td>EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)</td>
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<td>F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G&gt;A variant</td>
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<td>81241</td>
<td>F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant</td>
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<td>81242</td>
<td>FANCC (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>81243</td>
<td>FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles</td>
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<td>81244</td>
<td>FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and methylation status)</td>
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<td>FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)</td>
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<td>81246</td>
<td>FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)</td>
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<td>G6PC (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>81251</td>
<td>GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G&gt;A)</td>
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<td>GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence</td>
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<td>81253</td>
<td>GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants</td>
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<td>GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830]) and 232kb [del(GJB6-D13S1854)])</td>
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<td>81255</td>
<td>HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G&gt;C, G269S)</td>
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HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)

HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis 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)

IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)

IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)

IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (eg, Southern blot)

IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis

IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)

Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (eg, 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)

Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed
baseline analyses; without cell selection

81268 Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; with cell selection (eg, CD3, CD33), each cell type

81270 JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant

81272 KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)

81273 KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)

81275 KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)

81276 KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)

81281 Long QT syndrome gene analyses (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); known familial sequence variant (code deleted 1/1/2017)

81290 MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)

81287 MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis

81291 MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)

81292 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81288 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis

81293 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg,
hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81294 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81295 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81296 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81297 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81298 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81299 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81300 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81301 Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed

81302 MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis

81303 MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant

81304 MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants

81310 NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)

PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)

PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)

PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative

PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative

PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis

PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant

PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
81324  PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325  PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326  PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81330  SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81331  SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332  SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
81340  TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)
81341  TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (eg, Southern blot)
81342  TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81355  VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A,
c.173+1000C>T)

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

(See Considerations section)
Effective 2017, 81280 and 81282 were deleted.

Effective in 2013, 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.

Additional Policy Key Words
N/A

Policy Implementation/Update Information
2/1/15 New policy. If not a benefit exclusion, some may be considered medically necessary
2/1/16 No policy statement changes.
4/1/16 Policy updated with new categories of genetic testing. Medical necessity criteria revised for each new category of testing; for the category of testing an individual for the benefit of a family member, criteria are for clinical utility rather than medical necessity.
2/1/17 On the first medically necessary statement removed "Risk Assessment"
and added "Therapeutic" and on the second medically necessary policy statement removed "Testing to predict treatment response" and added "Therapeutic". No other policy statement changes.

4/1/17  No policy statement changes.

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Appendix 1

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 would be:

- Trial comparing outcomes with use of the test versus outcomes without use of the test
- Associational study of genetic testing with outcomes

Indirect Evidence
When direct evidence is not available, indirect evidence should be evaluated. Indirect evidence is evidence that addresses one 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 of these disorders are rare, and high-quality evidence on the efficacy of treatment for the disorder is often lacking. This is particularly true for aspects of management such as increased surveillance for complications, ancillary treatments (physical therapy, occupational therapy, etc.), and referrals to specialists. When evidence on outcomes is lacking, a consideration may be given as to whether these aspects of care are considered standard-of-care for that disorder, especially when they are part of guidelines by authoritative bodies.

There are a number of factors that influence the strength of indirect evidence that is needed to determine whether health outcomes are improved. None of these factors are by themselves determinative of whether genetic testing should be performed, but they may be important determinants of the potential clinical utility of testing. Some of these considerations are as follows:

I. Factors impacting the strength of indirect evidence for diagnostic testing

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
  - Moderate morbidity/disability
  - Minor or no morbidity/disability

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

Impact of genetic test on 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 the Initiation of other management changes with uncertain impact on outcomes (referrals to specialists and/or ancillary care, initiate screening, etc.)
  ▪ 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 A. Factors Influencing the Strength of an Indirect Chain of Evidence on Clinical Utility – Diagnostic Testing
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease Characteristics</th>
<th>Impact on Diagnosis</th>
<th>Impact on Management</th>
<th>Impact on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortened LE</td>
<td>Severe morbidity / disability</td>
<td>Confirms diagnosis</td>
<td>Rules out disorder</td>
<td>Initiate effective treatment for disorder</td>
</tr>
<tr>
<td></td>
<td>Moderate morbidity / disability</td>
<td>Condition defined by mutation</td>
<td>Contributes to ability to make diagnosis</td>
<td>Initiate other management changes</td>
</tr>
<tr>
<td></td>
<td>Minor or no morbidity / disability</td>
<td>Unable to make clinically</td>
<td>Eliminates need for other clinical work-up</td>
<td>Discontinue ineffective treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Provide standard of care treatment for disorder</td>
</tr>
</tbody>
</table>
II. Factors impacting the strength of indirect evidence for risk assessment testing

**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
  - Moderate morbidity/disability
  - Minor or no morbidity/disability
- Is there a presymptomatic phase during which a clinical diagnosis cannot be made?

**Impact of genetic test 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 mutation in the family?
- Is the penetrance of the genetic mutation known?
- Are there other factors that impact the clinical expression of disease?

**Impact of genetic test 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 test lead to the initiation of other management changes that may or may not lead to improved outcomes (referrals to specialists and/or ancillary care, initiate screening, etc.)
- Does a negative test confirm a lack of risk for the disease, and does this lead to “turning off” interventions, such as surveillance, that would otherwise be performed?
- Is it likely that knowledge of mutation 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

<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 LE</td>
<td>Severe morbidity / disability</td>
<td>Has presymptomatic stage</td>
<td>Initiate effective interventions in presymptomatic phase</td>
<td>Definite improved health outcomes</td>
</tr>
<tr>
<td></td>
<td>Moderate morbidity / disability</td>
<td>Determines risk in substantial proportion of patients</td>
<td>Other management changes with uncertain impact</td>
<td>Possible impact on outcomes, data lacking</td>
</tr>
<tr>
<td></td>
<td>Minor or no morbidity / disability</td>
<td>Known mutation in family</td>
<td>Negative test turns off interventions</td>
<td>Barriers to research</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Penetration is well known</td>
<td>Likely to impact reproductive decision making</td>
<td>Impact on lifestyle factors</td>
</tr>
</tbody>
</table>
III. Factors influencing the strength of indirect evidence for prognosis testing

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
  - Moderate morbidity/disability
  - Minor or no morbidity/disability

Impact of genetic test 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 test 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 change 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 – Prognostic Testing

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease Characteristics</th>
<th>Impact on Prognosis</th>
<th>Impact on Management</th>
<th>Impact on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortened LE</td>
<td>Severe morbidity / disability</td>
<td>Mutation associated with prognosis</td>
<td>Clinically credible prognostic groups</td>
<td>Definite improved health outcomes</td>
</tr>
<tr>
<td>Moderate morbidity / disability</td>
<td>Incremental improvement above clinical measures</td>
<td>Treatment by prognostic groups improve outcomes</td>
<td>Possible impact on outcomes, data lacking</td>
<td></td>
</tr>
<tr>
<td>Minor or no morbidity / disability</td>
<td>Contributing to ability to make diagnosis</td>
<td>Treatment by prognostic group is standard of care</td>
<td>Barriers to research</td>
<td></td>
</tr>
</tbody>
</table>

### IV. Factors influencing the strength of indirect evidence for genetic variants that alter response to treatment

**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
  - 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 that are 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 that are associated with increased risk for adverse effects?

Impact of genetic test 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 that are 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

<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 LE</td>
<td>Severe morbidity / disability</td>
<td>Moderate morbidity / disability</td>
<td>Minor or no morbidity / disability</td>
<td>Effective pharmacologic therapy</td>
</tr>
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