| MEDICAL POLICY | Genetic Studies and Counseling |
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| **Effective Date: 10/1/2021**<br>  <br>10/1/2021<br>Medical Officer Date | Medical Policy Number: 215<br>Medical Policy Committee Approved Date: 10/15; 6/16; 12/16; 11/17; 12/17; 1/18; 2/18; 4/18; 6/18; 8/18; 9/18; 12/18; 4/18; 5/19; 11/19; 07/2020; 12/2020; 03/2021; 09/2021 |

**See Policy CPT/HCPCS CODE section below for any prior authorization requirements**

## SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

## APPLIES TO:

All lines of business

## BENEFIT APPLICATION

Medicaid Members

*Oregon*: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

## DOCUMENTATION REQUIREMENTS

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request:

- Name of the panel test OR the name of the gene(s) and/or components of the test
- Name of laboratory that performed or is performing the test
- Clinical notes should include the following:
  - Reason for performing test, including the suspected condition
  - Signs/symptoms/test results related to reason for genetic testing
  - Family history, if applicable
  - How test results will impact clinical decision making
- CPT codes billed

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# POLICY CRITERIA

**Notes**:

- This document does not address the following:
  - Pharmacogenetic tests (testing to determine the appropriate course of therapy).
  - Genetic tests related to reproductive planning or prenatal testing.
- Other, more specific, Medical Policies may apply:
  - Please see Cross References section below for medical policies which may apply to specific conditions.
    For example, genetic testing for hereditary colorectal cancer is addressed in the *Genetic Testing: Inherited Susceptibility to Colorectal Cancer* medical policies.

**Policy Criteria Links**

- Genetic Counseling (For all lines of business except Medicare)
- General Criteria for Genetic Testing (All Lines of Business)
- Covered Genetic Testing (All Lines of Business)
  - Hereditary Hearing Loss
  - Li-Fraumeni Syndrome
  - Long QT Syndrome
  - Microarray Testing
- Non-Covered Genetic Testing (All Lines of Business)
- Covered Genetic Testing (Medicare Only)

**Genetic Counseling (For all lines of Business)**

I. The following general genetic counseling criteria must be met prior to genetic testing:

A. Provider is a board-eligible or board-certified genetic counselor or board-certified physician with training and ongoing experience in genetics* (see Policy Guidelines section below for complete list of appropriate providers); **and**
B. A full personal and family history has been conducted and is documented (when applicable); **and**
C. Genetic testing information and pre-test counseling has been provided and is documented; **and**
D. Patient has undergone and signed informed consent for genetic testing; **and**

E. Post-test counseling to review the test results and determine future evaluation, medical management and treatment plans has been discussed and will be scheduled, if applicable.

**General Criteria for Genetic Testing (All Lines of Business)**

For genetic testing not addressed in other, more specific PHP Medical Policies, the following medical necessity criteria may be applied:

II. Genetic testing may be considered **medically necessary and covered** when **ALL** of the following criteria (A.-D) are met:

A. The genetic counseling requirements above (criteria I.) have been met; **and**
B. The individual being tested meets **either** of the following criteria:
   1. The patient is symptomatic and the clinical presentation is consistent with a known condition; **or**
   2. The individual is asymptomatic and meets **either** of the following criteria:
      a. Individual has a first-degree blood relative (parent, sibling, or child) diagnosed with a condition **and** the affected relative has not had genetic testing and is unavailable for testing; **or**
      b. Testing is for a known pathogenic mutation confirmed in an affected first-degree blood relative (parent, sibling, or child); **and**
C. The condition being tested for is associated with increased morbidity or reduced life-expectancy; **and**
D. Clinical utility must be established for each gene and/or component of the test, including **both** of the following (1. and 2.):
   1. Testing allows for a definitive diagnosis or risk classification when other clinical and/or laboratory tests were inconclusive **or** avoids more invasive diagnostic testing (i.e., muscle biopsy); **and**
   2. Testing results will guide decision(s) in clinical management (predictive, diagnostic, prognostic, or therapeutic).

III. Genetic testing is considered **investigational and is not covered** when the above criteria II. are not met, including but not limited to general population-based screening.

IV. In patients 17 years of age or younger, genetic testing for adult-onset genetic conditions, in which treatment management occurs after 18 years of age, is considered **not medically necessary and is not covered**.

**Covered Genetic Testing (All Lines of Business)**

Hereditary Hearing Loss

V. Genetic testing for GJB2 and/or GJB6 is considered **medically necessary and covered** for diagnosis or management of hereditary hearing loss.

Li Fraumeni Syndrome

VI. For non-Medicare members, genetic testing of the TP53 gene may be considered **medically necessary and covered** for evaluation and diagnosis of Li-Fraumeni syndrome when **any of one** of the following are met:

A. Individual from a family with a known TP53 mutation; **or**
B. Classic Li-Fraumeni Syndrome criteria are met, including **all** of the following (1. -3.):
   1. Combination of an individual diagnosed < age 45 y with a sarcoma; **and**
   2. A first degree relative diagnosed < age 45 y with cancer; **and**
   3. An additional first- or second-degree relative in the same lineage with cancer diagnosed < age 45 y, or a sarcoma at any age; **or**
C. Chompret criteria are met, including **any one** of the following (1. -3.):
   1. Individual meets both of the following criteria (a. or b.):
      a. Individual with a tumor from LFS tumor spectrum (e.g. soft tissue sarcoma, osteosarcoma, brain tumor, breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) before age of 46 years, **and**
      b. At least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age; **or**
   2. Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years; **or**
   3. Individual with adrenocortical carcinoma or choroid plexus carcinoma at any age of onset, regardless of the family history; **or**
   4. Individual with breast cancer before 31 years.

VII. For non-Medicare members, genetic testing of the TP53 gene is considered **investigational and not covered** for all other indications, including but not limited to when the above criteria (VI.) are not met.

VIII. For Medicare members, TP53 gene testing is considered **not medically necessary and not covered.**[1,2]

Long QT Syndrome (LQTS)

IX. Genetic testing for LQTS may be considered **medically necessary and covered** in patients who do not meet clinical criteria for LQTS (e.g., Schwartz score <4) but who do meet one or more of the following criteria:
Note: Please see Policy Guidelines section below to calculate the Schwartz score.

A. A first-, second-, or third-degree relative with a known LQTS mutation; **or**
B. A first-, second-, or third-degree relative diagnosed with LQTS by clinical means whose genetic status is unavailable; **or**

C. Signs or symptoms indicating a moderate to high pretest probability of LQTS (e.g., Schwartz score of 2-3).

X. Genetic testing for LQTS is considered **investigational and not covered** when criterion IX. is not met, including but not limited to:

A. To determine prognosis and/or direct therapy in patients with known LQTS
B. For screening of the general population

Microarray Testing

XI. Microarray testing may be considered **medically necessary and covered** when both of the following criteria are met:

A. The patient must be under the care of a pediatric geneticist or developmental pediatrician who is the ordering physician; **and**
B. This patient must have **either** of the following conditions:
   1. Have unexplained developmental delay/intellectual disability; **or**
   2. Have multiple congenital anomalies.

Note: This policy does not address microarray testing for reproductive planning and prenatal purposes. Please see Genetic Testing: Reproductive Planning and Prenatal Testing policies in the Cross References section below.

**Non-Covered Genetic Testing (All Lines of Business)**

XII. The following are tests are considered **investigational and are not covered** due to lack of evidence of clinical benefit:

A. FirstStep Dx Plus
B. Genomic testing for Hematological Oncology Indications
C. MTHFR gene (This policy does not address MTHFR testing for inherited thrombophilias. Please see the Genetic Testing: Inherited Thrombophilias policies in the Cross References section below.)

XIII. Direct-to-consumer genetic tests are considered **investigational and not covered** for any situation or indication. (Please see Description section below for more information.)

XIV. Genetic panel testing is considered **investigational and not covered** if any component of the panel is considered investigational or not medically necessary.

**Covered Genetic Testing (Medicare Only)**

This section of the policy is based on several Centers for Medicare & Medicaid Services (CMS) Local Coverage Determinations (LCDs) and Local Coverage Articles (LCAs). Please refer to test-specific

CMS guidance documents for covered ICD-10 codes and medical necessity criteria when indicated. This CMS guidance was identified as of the last policy review date on 06/24/2020.

XIII. The following genetic panel tests may be considered **medically necessary and covered** for Medicare members:

A. CancerTYPE ID® (Biotheranostics): Covered for specific diagnosis codes only. LCAs: A54388, L36256[3,4]
B. OncotypeDx Colon Cancer (Genomic Health): Covered for specific diagnosis codes only. LCAs: A54486[5]
C. Tissue of Origin® (TOO®) (Cancer Genetics Inc., previously known as ResponseDX): Covered for specific diagnosis codes only. LCAs: A54496, A55204.[6,7]

# POLICY GUIDELINES

*Genetic Counseling Requirements

Genetic studies and counseling are approved subject to benefits when there is a medical condition that requires genetic counseling and potential subsequent testing to diagnose or to aid in planning a treatment course. Identification of a genetic disorder should result in medical and/or surgical management that is corrective and/or therapeutic in nature.

Prior to authorization of a genetic test, the member must have undergone pretest counseling by a certified genetic counselor or a provider trained in genetics. A provider trained in genetics is defined as providing risk assessment on a regular basis and having received specialized ongoing training in genetics. Education limited to learning how to order a test is not considered adequate training for risk assessment and genetic counseling. The provider may be required to provide documentation of genetic training and ongoing continual medical education (CME). Examples of providers trained in genetic counseling or genetics are:

- Board-Eligible or Board-Certified Genetic Counselor (CGC)
- Advanced Genetics Nurse (AGN-BC), Genetic Clinical Nurse (GCN)
- Advanced Practice Nurse in Genetics (APNG)
- Board-Eligible or Board-Certified Clinical Geneticist
- Board-Certified physician with training and ongoing experience in genetics (e.g., obstetrician–gynecologist; surgical oncologist; medical oncologist; fellowship-trained surgeon, pediatrician, family medicine.)

Clinical Utility

Clinical utility of any genetic test is established by evaluating the following components of the test:

- Eliminates the need for further clinical workup or invasive testing
- Leads to changes in clinical management of the condition that improve outcomes
- Leads to discontinuation of interventions that are unnecessary and/or ineffective

- Leads to initiation of effective medication(s) and/or changes in dosing of a medication that is likely to improve outcomes
- Leads to discontinuation of medications that are ineffective or harmful
- Provides prognostic information not revealed by standard laboratory and/or clinical testing that reclassifies patients into clinically relevant prognostic categories for which there are different treatment strategies

General Principles of Genetic Testing

All genetic tests must be Food and Drug Administration (FDA)-approved and/or performed in a Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory.

Schwartz score diagnostic criteria for long QT syndrome (LQTS)[8]

| | Points |
|---|---|
| **Electrocardiographic findings*** | |
| A. QTc[¶] | |
| ▪ ≥480 ms | 3 |
| ▪ 460 to 479 ms | 2 |
| ▪ 450 to 459 ms (in males) | 1 |
| B. QTc[¶] fourth minute of recovery from exercise stress test ≥480 ms | 1 |
| C. Torsades de pointes[Δ] | 2 |
| D. T wave alternans | 1 |
| E. Notched T wave in 3 leads | 1 |
| F. Low heart rate for age[◊] | 0.5 |
| **Clinical history** | |
| A. Syncope[Δ] | |
| ▪ With stress | 2 |
| ▪ Without stress | 1 |
| B. Congenital deafness | 0.5 |
| **Family history** | |
| A. Family members with definite LQTS[§] | 1 |
| B. Unexplained sudden cardiac death below age 30 among immediate family members[§] | 0.5 |

Score:

- ≤1 point = low probability of long QT syndrome (LQTS).
- 1.5 to 3 points = intermediate probability of LQTS.
- ≥3.5 points = high probability of LQTS.

Key:
* In the absence of medications or disorders known to affect these electrocardiographic features.
¶ QTc calculated by Bazett's formula where QTc = QT/√RR.
Δ Mutually exclusive.
◊ Resting heart rate below the second percentile for age.
§ The same family member cannot be counted in A and B.

## BILLING GUIDELINES

Some, but not all genetic tests may have a specific CPT or HCPCS code assigned. Some panels may be billed with unlisted codes (e.g.81479 or 81599) while others may be billed with multiple gene-specific and/or molecular pathology procedure codes (81400-81408).

## CPT/HCPCS CODES

Note: Codes which may be billed for genetic testing addressed in this policy include, but are not limited to, the following:

| All Lines of Business | |
|---|---|
| Prior Authorization Required | |
| ~~0081U~~ | TERMED 12/31/19<br>~~Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping genes), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis~~ |
| 0195U | KLF1 (Kruppel-like factor 1), targeted sequencing (ie, exon 13) |
| 0231U | CACNA1A (calcium voltage-gated channel subunit alpha 1A) (eg, spinocerebellar ataxia), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) gene expansions, mobile element insertions, and variants in non-uniquely mappable regions |
| 0232U | CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions |
| 0233U | FXN (frataxin) (eg, Friedreich ataxia), gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions |
| 0234U | MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions |

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| 0235U | PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions |
| 0236U | SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications and deletions, and mobile element insertions |
| 0237U | Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), genomic sequence analysis panel including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions |
| 0238U | Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions |
| 0269U | Hematology (autosomal dominant congenital thrombocytopenia), genomic sequence analysis of 14 genes, blood, buccal swab, or amniotic fluid |
| 81105 | Human Platelet Antigen 1 genotyping (HPA-1), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa], antigen CD61 [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-1a/b (L33P) |
| 81106 | Human Platelet Antigen 2 genotyping (HPA-2), GP1BA (glycoprotein Ib [platelet], alpha polypeptide [GPIba]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-2a/b (T145M) |
| 81107 | Human Platelet Antigen 3 genotyping (HPA-3), ITGA2B (integrin, alpha 2b [platelet glycoprotein IIb of IIb/IIIa complex], antigen CD41 [GPIIb]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-3a/b (I843S) |
| 81108 | Human Platelet Antigen 4 genotyping (HPA-4), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa], antigen CD61 [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-4a/b (R143Q) |
| 81109 | Human Platelet Antigen 5 genotyping (HPA-5), ITGA2 (integrin, alpha 2 [CD49B, alpha 2 subunit of VLA-2 receptor] [GPIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant (eg, HPA-5a/b (K505E)) |
| 81110 | Human Platelet Antigen 6 genotyping (HPA-6w), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa, antigen CD61] [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-6a/b (R489Q) |
| 81111 | Human Platelet Antigen 9 genotyping (HPA-9w), ITGA2B (integrin, alpha 2b [platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41] [GPIIb]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-9a/b (V837M) |
| 81112 | Human Platelet Antigen 15 genotyping (HPA-15), CD109 (CD109 molecule) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-15a/b (S682Y) |

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| 81120 | IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C) |
| 81161 | DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed |
| 81163 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis |
| 81165 | BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis |
| 81171 | AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles |
| 81172 | AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status) |
| 81173 | AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; full gene sequence |
| 81174 | AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant |
| 81175 | ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence |
| 81176 | ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12) |
| 81177 | ATN1 (atrophin 1) (eg, dentatorubral-pallidoluysian atrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81178 | ATXN1 (ataxin 1) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81179 | ATXN2 (ataxin 2) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81180 | ATXN3 (ataxin 3) (eg, spinocerebellar ataxia, Machado-Joseph disease) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81181 | ATXN7 (ataxin 7) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81182 | ATXN8OS (ATXN8 opposite strand [non-protein coding]) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81183 | ATXN10 (ataxin 10) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81184 | CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; evaluation to detect abnormal (eg, expanded) alleles |
| 81185 | CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; full gene sequence |
| 81186 | CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; known familial variant |
| 81187 | CNBP (CCHC-type zinc finger nucleic acid binding protein) (eg, myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |

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| 81188 | CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles |
| 81189 | CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; full gene sequence |
| 81190 | CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; known familial variant(s) |
| 81204 | AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; characterization of alleles (eg, expanded size or methylation status) |
| 81219 | CALR (calreticulin)(eg myeloproliferative disorders, gene analysis, common variants in exon 9) |
| 81228 | Cytogenomic constitutional (gnome-wide) microarray analysis; interrogation of genomic common variants regions for copy number variants (e.g. Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization[CGH] microarray analysis) |
| 81233 | BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F) |
| 81234 | DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles |
| 81236 | EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence |
| 81237 | EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646) |
| 81238 | F9 (coagulation factor IX) (eg, hemophilia B), full gene sequence |
| 81239 | DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; characterization of alleles (eg, expanded size) |
| 81247 | G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-) |
| 81248 | G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s) |
| 81249 | G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence |
| 81250 | G6PC (glucose-6-phosphatase, catalytic subunit) (e.g., Glycogen storage disease, type 1a, von Gierke disease) gene analysis, common variants (e.g., R83C, Q347X) |
| 81256 | HFE (hemochromatosis) (e.g. hereditary hemochromatosis) gene analysis, common variants (e.g. C282Y, H63D) |
| 81257 | HBA1/HBA2 (alpha globin 1 and alpha globin 2)(e.g. alpha thalsemmia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha20.5, and Constant Spring) |
| 81258 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant |
| 81259 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence |
| 81269 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants |
| 81271 | HTT (huntingtin) (eg, Huntington disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles |

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| 81274 | HTT (huntingtin) (eg, Huntington disease) gene analysis; characterization of alleles (eg, expanded size) |
| 81284 | FXN (frataxin) (eg, Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles |
| 81285 | FXN (frataxin) (eg, Friedreich ataxia) gene analysis; characterization of alleles (eg, expanded size) |
| 81286 | FXN (frataxin) (eg, Friedreich ataxia) gene analysis; full gene sequence |
| 81289 | FXN (frataxin) (eg, Friedreich ataxia) gene analysis; known familial variant(s) |
| 81305 | MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant |
| 81311 | 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) |
| 81315 | 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 |
| 81316 | 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 |
| 81312 | PABPN1 (poly[A] binding protein nuclear 1) (eg, oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81321 | PTEN (phosphatase and tensin)(e.g., Cowden Syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis |
| 81322 | PTEN (phosphatase and tensin)(e.g., Cowden Syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant |
| 81323 | PTEN (phosphatase and tensin)(e.g., Cowden Syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant |
| 81324 | PMP22 (peripheral myelin protein 22)(e.g., Charcot-Marie-Tooth hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis |
| 81325 | PMP22 (peripheral myelin protein 22)(e.g., Charcot-Marie-Tooth hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence |
| 81326 | PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth hereditary neuropathy with liability to pressure palsies) gene analysis; know familial variant |
| 81327 | SEPT9 (Septin9) (eg, colorectal cancer) methylation analysis |
| 81329 | SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed |
| 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 | SERPINA 1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase variants (e.g., *S and *Z) |
| 81333 | TGFBI (transforming growth factor beta-induced) (eg, corneal dystrophy) gene analysis, common variants (eg, R124H, R124C, R124L, R555W, R555Q) |

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| 81334 | RUNX1 (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (eg, exons 3-8) |
| 81336 | SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence |
| 81337 | SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s) |
| 81343 | PPP2R2B (protein phosphatase 2 regulatory subunit Bbeta) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81344 | TBP (TATA box binding protein) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81345 | TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region) |
| 81347 | SF3B1 (splicing factor [3b] subunit B1) (eg, myelodysplastic syndrome/acute myeloid leukemia) gene analysis, common variants (eg, A672T, E622D, L833F, R625C, R625L) |
| 81348 | SRSF2 (serine and arginine-rich splicing factor 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L) |
| 81357 | U2AF1 (U2 small nuclear RNA auxiliary factor 1) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, S34F, S34Y, Q157R, Q157P) |
| 81400 | Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis) |
| 81401 | Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) |
| 81402 | Molecular pathology procedure, level 3 (e.g.,>10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants 1 exon) |
| 81403 | Molecular pathology procedure, level 4 (e.g. analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons |
| 81404 | Molecular pathology procedure, level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder /triplet repeat by southern blot analysis |
| 81405 | Molecular pathology procedure, level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons) |
| 81406 | Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) |
| 81407 | Molecular pathology procedure, level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) |
| 81408 | Molecular pathology, level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis) |
| 81413 | Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence |

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| | analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A |
| 81414 | Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1 |
| 81415 | Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis |
| 81416 | Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure) |
| 81417 | Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome) |
| 81419 | Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2 |
| 81430 | Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1 |
| 81431 | Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes |
| 81434 | Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A |
| 81437 | Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL |
| 81438 | Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL |
| 81439 | Hereditary cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (eg, DSG2, MYBPC3, MYH7, PKP2, TTN) |
| 81442 | Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1 |

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| 81448 | Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1) |
| 81595 | Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as a rejection risk score |
| S3870 | Comparative genomic hybridization (cgh) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability |
| No Prior Authorization Required | |
| 0023U | Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin |
| 0046U | FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative |
| 81164 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements) |
| 81166 | BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements) |
| 81167 | BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements) |
| 81218 | CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence |
| 81229 | Cytogenomic constitutional (gnome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities |
| 81252 | GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence |
| 81253 | GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants |
| 81254 | 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)]) |
| 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) |
| 81301 | 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 |
| 81314 | PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18) |
| 88241 | Thawing and expansion of frozen cells, each aliquot |

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| 88245 | Chromosome analysis for breakage syndromes; baseline sister chromatid exchange, 20-25 cells |
| 88248 | Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (e.g., for ataxia telangiectasia, fanconi anemia, fragile X) |
| 88249 | Chromosome analysis for breakage syndromes; baseline breakage, score 100 cells, clastogen stress (e.g. Diepoxybutane, mitomycin C, ionizing radiation, UV radiation |
| 88261 | Chromosome analysis; count 5 cells, l karyotype, with banding |
| 88263 | Chromosome analysis; count 45 cells for mosaicism, 2 Karyotypes, with banding |
| 88271 | Molecular cytogenetics; DNA probe, each |
| 88272 | Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (e.g. for derivatives and markers) |
| 88274 | Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells |
| 88275 | Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells |
| 88283 | Chromosome analysis; additional specialized banding technique (e.g., NOR, C-banding) |
| 88285 | Chromosome analysis; additional cells counted, each study |
| 88289 | Chromosome analysis; additional high resolution study |
| 88291 | Cytogenetics and molecular cytogenetics, interpretation and report |
| S3844 | DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness |
| Not Covered | |
| 0049U | NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative |
| 81291 | MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C) |
| 81306 | NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *3, *4, *5, *6) |
| 81320 | PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F) |
| 81535 | Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination |
| 81536 | Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; each additional single drug or drug combination (List separately in addition to code for primary procedure) |
| 81538 | Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival |
| Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then **prior-authorization is required.** | |
| 81479 | Unlisted Molecular Pathology |
| 81599 | Unlisted multianalyte assay with algorithmic analysis |

| All Lines of Business Except Medicare | |
|---|---|
| Prior Authorization Required | |
| 81121 | IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M) |
| 81200 | ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g., E285A, Y231X) |
| 81205 | BCKDHB (branched-chain keto acid dehyrogenase E1, beta polypeptide) (e.g., Maple syrup urine disease) gene analysis, common variants (e.g., R183P, G278s, E422X) |
| 81209 | BLM (Bloom syndrome, RecQ helicase-like) (e.g., Bloom syndrome) gene analysis 2281 del6ins7 variant |
| 81210 | BRAF(v-raf murine sarcoma viral oncogene homolog B1) (e.g. Colon Cancer) gene analysis, V600E variant |
| 81235 | 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) |
| 81242 | FANCC (Fanconi anemia, complementation group C) (e.g., Fanconi Anemia, type C) gene analysis, common variant (e.g., IVS4=4A>T) |
| 81243 | FMR1 (Fragile X mental retardation 1) (e.g., fragile x mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles |
| 81244 | FMR1 (Fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and methylation status) |
| 81251 | GBA (glucosidase, bets, acid) (e.g., Gaucher disease) gene analysis, common variants (e.g., N370S, 84GG, L444P, IVS2=1G>A) |
| 81255 | HEXA (hexosaminidase A [alpha polypeptide]) (e.g. Tay-Sachs disease) gene analysis common variants (e.g., 1278insTATC, 1421+1G>C, G269S) |
| 81260 | IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein)(e.g. familial dysautonomia) gene analysis, common variants |
| 81275 | KRAS ((V-KI-RAS2 Kirsten Rat Sarcoma Viral Oncogene)( EG carcinoma) gene analysis, variants in codons 12 and 13 |
| 81276 | KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146) |
| 81290 | MCOLN1 (mucolipin 1 ) (e.g., Mucolipidosis, Type IV) gene analysis, common variants (e.g. IVS3-2A>G, del6.4b) |
| 81302 | MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; full sequence analysis |
| 81303 | MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; known familial variant |
| 81304 | MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; duplication/deletion variants 6 or exon 6), qualitative or quantitative |
| 81330 | SMPD1 (sphingomyelin phosphodiesterase 1, acid lysomal) (e.g., Niemann-Pick disease Type A) gene analysis, common variants (e.g., R496L, L302P, fsP330) |
| 81361 | HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE) |
| 81362 | HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s) |

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| 81363 | HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s) |
| 81364 | HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence |
| 81412 | Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1 |
| 81443 | Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH) |

### Not Covered

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| 0037U | Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden |
| 81504 | Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores |
| 81525 | Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score |
| 81540 | Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype |

## Medicare Only

### Prior Authorization Required

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| 0244U | Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue |
| 0258U | Autoimmune (psoriasis), mRNA, next generation sequencing, gene expression profiling of 50-100 genes, skin-surface collection using adhesive patch, algorithm reported as likelihood of response to psoriasis biologics |
| 0260U | Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping |
| 0264U | Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping |

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| 0266U | Unexplained constitutional or other heritable disorders or syndromes, tissue specific gene expression by whole transcriptome and next-generation sequencing, blood, formalin-fixed paraffin embedded (FFPE) tissue or fresh frozen tissue, reported as presence or absence of splicing or expression changes |
| 0268U | Hematology (atypical hemolytic uremic syndrome [aHUS]), genomic sequence analysis of 15 genes, blood, buccal swab, or amniotic fluid |
| 0271U | Hematology (congenital neutropenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid |
| 0273U | Hematology (genetic hyperfibrinolysis, delayed bleeding), genomic sequence analysis of 8 genes (F13A1, F13B, FGA, FGB, FGG, SERPINA1, SERPINE1, SERPINF2, PLAU), blood, buccal swab, or amniotic fluid |
| 0274U | Hematology (genetic platelet disorders), genomic sequence analysis of 43 genes, blood, buccal swab, or amniotic fluid |
| 0276U | Hematology (inherited thrombocytopenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid |
| 0277U | Hematology (genetic platelet function disorder), genomic sequence analysis of 31 genes, blood, buccal swab, or amniotic fluid |
| No Prior Authorization Required | |
| 81121 | IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M) |
| 81210 | BRAF(v-raf murine sarcoma viral oncogene homolog B1) (e.g. Colon Cancer) gene analysis, V600E variant |
| 81235 | 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) |
| 81245 | FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15) |
| 81246 | FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836) |
| 81275 | KRAS ((V-KI-RAS2 Kirsten Rat Sarcoma Viral Oncogene)( EG carcinoma) gene analysis, variants in codons 12 and 13 |
| 81276 | KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146) |
| 81504 | Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores |
| 81525 | Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score |
| 81540 | Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype |
| Not Covered | |
| 81200 | ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g., E285A, Y231X) |

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| 81205 | BCKDHB (branched-chain keto acid dehyrogenase E1, beta polypeptide) (e.g., Maple syrup urine disease) gene analysis, common variants (e.g., R183P, G278s, E422X) |
| 81209 | BLM (Bloom syndrome, RecQ helicase-like) (e.g., Bloom syndrome) gene analysis 2281 del6ins7 variant |
| 81242 | FANCC (Fanconi anemia, complementation group C) (e.g., Fanconi Anemia, type C) gene analysis, common variant (e.g., IVS4=4A>T) |
| 81243 | FMR1 (Fragile X mental retardation 1) (e.g., fragile x mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles |
| 81244 | FMR1 (Fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and methylation status) |
| 81251 | GBA (glucosidase, bets, acid) (e.g., Gaucher disease) gene analysis, common variants (e.g., N370S, 84GG, L444P, IVS2=1G>A) |
| 81255 | HEXA (hexosaminidase A [alpha polypeptide]) (e.g. Tay-Sachs disease) gene analysis common variants (e.g., 1278insTATC, 1421+1G>C, G269S) |
| 81260 | IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein)(e.g. familial dysautonomia) gene analysis, common variants |
| 81290 | MCOLN1 (mucolipin 1 ) (e.g., Mucolipidosis, Type IV) gene analysis, common variants (e.g. IVS3-2A>G, del6.4b) |
| 81302 | MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; full sequence analysis |
| 81303 | MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; known familial variant |
| 81304 | MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; duplication/deletion variants 6 or exon 6), qualitative or quantitative |
| 81330 | SMPD1 (sphingomyelin phosphodiesterase 1, acid lysomal) (e.g., Niemann-Pick disease Type A) gene analysis, common variants (e.g., R496L, L302P, fsP330) |
| 81361 | HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE) |
| 81362 | HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s) |
| 81363 | HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s) |
| 81364 | HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence |
| 81412 | Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1 |
| 81443 | Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH) |

## DESCRIPTION

A genetic test is "the analysis of human deoxyribonucleic acid (DNA), ribonucleic acid (RNA) Chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes". Genetic tests may be used to detect newborn or adult genetic disease. The tests should aid in the diagnosis or in the treatment of a disorder. Genetic tests should have proven analytical validity along with clinical utility and validity, as evidenced in peer-reviewed literature.

The following section describes some of the tests addressed in this policy.

Li Fraumeni Syndrome (LFS)

LFS is an extremely rare autosomal-dominant mutation of the p53 tumor suppressor gene. Persons with LFS have an approximately 25-fold increased risk of developing a malignant tumor by age 50 than the population average, and are at risk for a wide range of malignancies, with particularly high occurrences of breast cancer, brain tumors, acute leukemia, sarcomas and adrenal cortical carcinoma.

Long QT Syndrome (LQTS)

The Familion genetic panel test is one example of genetic testing for LQTS. This panel analyzes all coding exons of 5 major cardiac ion channel genes: KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3; BS1), KCNE1 (LQT5), and KCNE2 (LQT6). A family-specific analysis that provides an examination of a previously known familial variant is also available. The target population is individuals with suspected familial LQTS, as well as asymptomatic relatives of individuals who have tested positive for a genetic variant for one of the LQTS genes. Direct DNA sequencing is performed using the polymerase chain reaction (PCR), followed by sequence analysis using an automated DNA sequencer. A reference database is used to analyze the sequence traces for both heterozygous and homozygous variants.

MTHFR Gene

The MTHFR gene provides instructions for making an enzyme called methylenetetrahydrofolate reductase. This enzyme plays a role in processing amino acids, the building blocks of proteins. Methylenetetrahydrofolate reductase is important for a chemical reaction involving forms of the B-vitamin folate (also called folic acid or vitamin B9). Specifically, this enzyme converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. This reaction is required for the multistep process that converts the amino acid homocysteine to another amino acid, methionine. The body uses methionine to make proteins and other important compounds.

Polymorphisms in the MTHFR gene have also been studied as possible risk factors for a variety of common conditions. These include heart disease, stroke, high blood pressure (hypertension), an eye disorder called glaucoma, psychiatric disorders, and certain types of cancer. This test has been commonly ordered but there are no proven benefits from the MTHRF testing. Therefore, it remains unclear what role changes in the MTHFR gene play in determining the risk of these complex conditions.

Direct-to-Consumer Testing

Direct-to-consumer (DTC) testing, also known as self-testing, at-home testing, or over the counter testing, are genetic tests that are sold directly to individuals via the Internet, television, print advertisements or other marketing materials. DTC tests are bought and performed with little to no involvement of a physician, genetic counselor, or other healthcare professional. After the individual places the order, a test kit is mailed to the individual who collects a sample typically by buccal swab or saliva. The sample is returned by mail to the lab and the results are provided directly to the individual via a website, mail or telephone.

There are a number of government agencies, including the Centers for Disease Control and Prevention (CDC), the National Institutes of Health: National Library of Medicine (NIH:NLM), and the Federal Trade Commission (FTC) who have expressed concerns regarding the risks and limitations of DTC tests.[9-11] These concerns are supported by major medical associations, including the American College of Human genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP).[12,13]

Concerns raised include lack of Clinical Laboratory Improvement Amendments (CLIA) accreditation for the testing laboratory and lack of appropriately educated (and board-certified) medical professionals employed by the company. There are also concerns that the limitations of the test will not be adequately explained to consumers, thereby allowing for medical and reproductive decisions without a complete understanding of the risks/benefits. In addition, there are security concerns regarding privacy and safety of personal and family information. Lastly, there is a paucity of evidence regarding the clinical utility of these tests.

OncotypeDx Colon Cancer

The OncotypeDx Colon Cancer test is a multigene expression assay for predicting recurrence of colon cancer, based on an individual patient's colon tumor expression of 12 genes, which quantifies the likelihood of recurrence in stage II colon cancer following surgery.

## INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

## REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

## MEDICAL POLICY CROSS REFERENCES

- Genetic Testing: *JAK2, CALR,* and *MPL* (All Lines of Business Except Medicare), GT400
- Genetic Testing: *JAK2, CALR,* and *MPL* (Medicare Only), GT399
- Genetic Testing: CADASIL Disease (All Lines of Business Except Medicare), GT405
- Genetic Testing: CADASIL Disease (Medicare Only), GT406
- Genetic Testing: Hereditary Breast and Ovarian Cancer: Genetic Counseling and Testing (All Lines of Business Except Medicare), GT155
- Genetic Testing: Hereditary Breast and Ovarian Cancer: Genetic Counseling and Testing (Medicare Only), GT380
- Genetic Testing: Inherited Susceptibility to Colorectal Cancer (All Lines of Business Except Medicare), GT388
- Genetic Testing: Inherited Susceptibility to Colorectal Cancer (Medicare Only), GT413
- Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare), GT401
- Genetic Testing: Inherited Thrombophilias (Medicare Only), GT402
- Genetic Testing: Non-Covered Genetic Panel Tests (All Lines of Business Except Medicare), GT235
- Genetic Testing: Non-Covered Genetic Panel Tests (Medicare Only), GT420
- Genetic Testing: Pharmacogenetic Testing (All Lines of Business Except Medicare), GT306
- Genetic Testing: Pharmacogenetic Testing (All Lines of Business Except Medicare), GT423
- Genetic Testing: Reproductive Planning and Prenatal Testing (All Lines of Business Except Medicare), GT236
- Genetic Testing: Reproductive Planning and Prenatal Testing (Medicare Only), GT384
- Genetic Testing: Whole Exome, Whole Genome and Proteogenomic Testing, GT389

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