Genetic and Molecular Testing

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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 Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. 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. 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.

SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☒ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP 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.

Notice to Medicaid Policy Readers: For comprehensive rules and guidelines pertaining to this policy, readers are advised to consult the Oregon Health Authority. It is essential to ensure full understanding and compliance with the state's regulations and directives. Please refer to OHA's prioritized list for the following coverage guidelines:

Medicaid members must also meet the genetic testing criteria governed by the Oregon Health Plan (OHP) Prioritized List Guideline Notes D1 and D17.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Criteria Table of Contents

- General Medical Necessity Criteria for Genetic and Molecular Testing
- Connective Tissue Disorders
- Familial Hypercholesterolemia
- Hereditary Peripheral Neuropathies
- Hypopituitarism
- Non-Syndromic Forms of Hearing Loss
- Not Medically Necessary Criteria

General Medical Necessity Criteria

I. Genetic and molecular testing (see Policy Guidelines for some examples) may be considered **medically necessary** when all of the following criteria (A.-D) are met:

A. Genetic Counseling general requirements have been met; **and**
B. The individual being tested meets **either** of the following criteria (1.-2.):

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 variant 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 is established for tests as demonstrated by both of the following:
    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 (e.g., muscle biopsy); **and**
    2. Testing results will guide decision(s) in clinical management (predictive, diagnostic, prognostic, or therapeutic).

Specific Indications

Connective Tissue Disorders

II. Genetic testing for connective tissue disorders may be considered **medically necessary** when the following criteria are met:
    A. Criterion I. above is met; **and**
    B. Either of the following are met:
        1. Genetic testing is used to diagnose a member with specific signs and symptoms of a connective tissue disorder (see Policy Guidelines for examples); **or**
        2. Genetic testing is for an asymptomatic member when there is a known pathogenic variant in the family.

Familial Hypercholesterolemia

III. Genetic testing for the management and evaluation of familial hypercholesterolemia may be considered **medically necessary** when all of the following are met (A.-C.):

    A. Criterion I. above is met; **and**
    B. Genes tested are limited to *APOB, LDLR, LDLRAP1* and/or *PCSK9* (single genes or any combination of the aforementioned); **and**
    C. Signs and symptoms are suggestive of familial hypercholesterolemia though a diagnosis has not yet been established via molecular diagnostics.

IV. Additional gene testing for management and evaluation of familial hypercholesterolemia (such as Comprehensive Lipidemia Panel (Invitae)) is considered **not medically necessary**.

V. Genetic testing for the management and evaluation of familial hypercholesterolemia is considered **not medically necessary** when the above criteria are not met.

Hereditary Peripheral Neuropathies

VI. Genetic testing to diagnose an inherited peripheral neuropathy, via targeted panel testing (see Policy Guidelines), may be considered **medically necessary** when all of the following are met (A.-C.):

1. Criterion I. above is met; **and**
2. When an individual has signs and/or symptoms of an inherited peripheral motor or sensory neuropathy; **and**
3. One of the following is met (1.-2.):
    1. A definitive clinical diagnosis cannot be made; **or**
    2. A genetic diagnosis is needed to inform reproductive planning.

VII. Genetic testing to diagnose an inherited peripheral neuropathy is considered **not medically necessary** when criterion VI. above is not met, including but not limited to non-targeted panels (see Policy Guidelines).

Hypopituitarism

VIII. Genetic testing for growth hormone (GH) deficiency, hypopituitarism and/or combined pituitary hormone deficiency may be **medically necessary** in members with GH deficiency and at least one other pituitary hormone deficiency that have met all of Criterion I.

Macrocephaly and Overgrowth

IX. Overgrowth and macrocephaly gene testing (e.g. Overgrowth and Macrocephaly Gene Panel (Prevention Genetics); Syndromic Macrocephaly/Overgrowth panel (GeneDx); Megalencephaly Panel (Seattle Children's Hospital)) may be considered **medically necessary** for the diagnosis and treatment of macrocephaly when all of the following are met (A.-C.):

A. Criterion I. above is met; **and**
B. Child presents with macrocephaly defined by any of the following (1.-3.):
    1. OFC > 97TH percentile for age, sex and gestation; **or**
    2. Serial OFC measurements with progressive enlargement; **or**
    3. Infant <6 months of age and OFC increases > 2cm (0.8 inches) per month; **and**
C. Either of the following is met (1.-2.):
    1. Child has features in the history or physical examination that suggest a multisystem or syndromic diagnosis (e.g. neurocutaneous findings, cutaneous or oral fibromas, hemangiomas); **or**
    2. Both of the following are met (a.-b.):
        a. The child has neurologic abnormalities or delayed development that requires intervention; **and**

b. Neuroimaging identifies enlarged cerebral structures.

X. Overgrowth and macrocephaly gene testing is considered not medically necessary when criterion IX. above is not met.

Non-Syndromic Forms of Hearing Loss

XI. Comprehensive genetic testing or next generation sequencing for diagnosing hearing loss in children may be considered **medically necessary** in children with bilateral sensorineural hearing loss without syndromic findings if patient also meets Criterion I. For members with clinical findings that suggest a specific genetic syndrome, targeted genetic testing should be performed to evaluate the specific syndrome.

XII. Genetic panel testing or next generation sequencing for diagnosing hearing loss is considered **not medically necessary** in patients with nonsyndromic **unilateral** hearing loss.

Not Medically Necessary Testing

XIII. Genetic and molecular testing is considered **not medically necessary** when there is insufficient evidence to demonstrate that the testing target or strategy has clinical utility (See Policy Guidelines).

XIV. Genetic and molecular testing is considered **not medically necessary** when the criteria above are not met.

XV. Repeat testing of the same germline genetic content, for the same genetic information, is considered **not medically necessary**.

Link to Evidence Summary

POLICY CROSS REFERENCES

- Cardiac Disease Risk Screening
- Circulating Tumor Cell and DNA Assays for Cancer Management
- Direct to Consumer and Over the Counter Testing
- Genetic Counseling
- Genetic Testing for CADASIL Disease
- Genetic Testing for Diagnostic Evaluation of Interstitial Lung Disease
- Genetic Testing for Hereditary Breast, Ovarian and Pancreatic Cancer
- Genetic Testing for Inherited Susceptibility to Colorectal Cancer
- Genetic Testing for Inherited Thrombophilias
- Genetic Testing for Myeloproliferative Diseases
- Non-Covered Genetic Panel Tests
- Genetic Testing for Reproductive Planning and Prenatal Testing
- Genetic Testing for Thyroid Nodules

- Whole Exome, Whole Genome and Proteogenomic Sequencing and Genetic Testing for Mitochondrial Disorders
- Serologic Testing and Therapeutic Monitoring for Inflammatory Bowel Disease
- Measurement of Antibodies to Immunosuppressive Therapies for Inflammatory Bowel Disease
- Next Generation Sequencing for Minimal Residual Disease Detection
- Non-Small Cell Lung Cancer: Tumor Testing for Targeted Therapy
- Multimarker Serum Testing for Ovarian Cancer
- Vectra DA Test for Rheumatoid Arthritis

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

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. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom-built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted
- Clinical notes to include the following:
  - Reason (indication) for performing test, including the suspected condition
  - Existing signs and/or symptoms related to reason for current test request
  - Prior test/laboratory results related to reason for current test request
  - Family history, if applicable
  - How results from current test request will impact clinical decision making
- All relevant CPT/HCPCS codes billed

DEFINITIONS

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.

Specific Indications

Connective Tissue Disorders

Heritable disorders of connective tissue (HDCTs) are a heterogeneous group of many inherited disorders and subtypes. Two of the most common HDCTs, Marfan syndrome (MFS) and the Ehlers-Danlos syndromes (EDS). HDCTs are a complex group of disorders that can be difficult to diagnose. Since their genetic basis is heterogenous, the incidence of an individual HDCT can range from commonly occurring—for example, hypermobility spectrum disorders (HSD)—to rare recessively inherited disorders. Variable expressivity, another standard concept in medical genetics, is also a hallmark of the HDCTs. This term denotes the different degrees of severity that may be seen in individuals carrying the same pathogenic DNA variant, even among members of the same family. Much work is still necessary to develop a full understanding of the gene–gene and gene–environment (e.g., tobacco use) interactions that contribute to the wide variation in expression seen in Mendelian genetic disorders.

Table 1: Signs and Symptoms of Connective Tissue Disorders
The most common signs and symptoms of connective tissue disorders are listed below with examples of frequently occurring symptoms (list is not exhaustive):

Connective Tissue Disorder	Symptoms
Ehlers-Danlos syndrome (EDS), type IV, also referred to as vascular EDS (vEDS)	Arterial aneurysms, dissection, or rupture; intestinal rupture; uterine rupture during pregnancy; and family history of vEDS. Additionally, thin, translucent skin; facial characteristics including thin lips, micrognathia, narrow nose, and prominent eyes; acrogeria; carotid-cavernous sinus arteriovenous fistula; and hypermobility of small joints.
Loeys-Dietz syndrome (LDS)	Vascular, skeletal, cardiofacial, cutaneous, allergic/inflammatory disease, and ocular manifestations. Aortic root dilatation is seen in more than 95% of probands.
Marfan syndrome (MFS)	Mild to severe manifestations of the ocular, skeletal, and cardiovascular systems. Myopia; bone overgrowth and joint laxity; disproportionately long extremities for the size of the trunk; pectus excavatum or pectus carinatum; and varying degrees of scoliosis.
Heritable thoracic aortic disease	Manifestations of the ocular, neurological, cardiovascular, and pulmonary systems

Familial Hypercholesterolemia

Familial hypercholesterolemia is a genetic disorder characterized by high cholesterol levels, specifically high levels of low-density lipoprotein (LDL) cholesterol, which is often referred to as "bad" cholesterol. This condition arises due to mutations in genes that are involved in the clearance of LDL cholesterol from the blood. As a result, people with familial hypercholesterolemia are at an increased risk of developing early cardiovascular diseases such as heart attacks and strokes. This condition is typically inherited in an autosomal dominant manner, meaning a single copy of the mutated gene from one affected parent can lead to the disorder. Treatment often involves lifestyle modifications, medications to lower cholesterol levels, and regular monitoring.

Macrocephaly and Overgrowth

Macrocephaly refers to a condition where an individual has an abnormally large head, which is typically defined as a head circumference that is greater than two standard deviations above the mean for their age and sex. This condition can be caused by various factors, including genetic disorders, increased brain volume, or other medical conditions. Overgrowth is a term used to describe excessive growth, which can affect the entire body or specific parts of the body. It can be caused by genetic disorders, hormonal imbalances, or other medical conditions. Overgrowth can lead to various health issues depending on which parts of the body are affected and the underlying cause of the overgrowth.

Nonsyndromic Hearing Loss

Nonsyndromic hearing loss is a partial or total loss of hearing that is not associated with other signs and symptoms.[1]

Syndromic Hearing Loss

Syndromic hearing loss occurs with signs and symptoms affecting other parts of the body.[1] Some of the more commonly known syndromes that present with hearing loss include:

- Alport
- Branchio-Oto-Renal (BOR)
- Charcot Marie Tooth
- Pendred
- Goldenhar
- Jervell and Lange-Neilsen
- Stickler
- Usher
- Turner
- Waardenburg
- Treacher Collins

BACKGROUND

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.[2] The tests should aid in the diagnosis or in the treatment of a

disorder, including screening in appropriate populations. Genetic tests should have proven analytical validity along with clinical utility and validity, as evidenced in peer-reviewed literature.

Certain technologies, some of which are new and emerging, allow for testing multiple targets and/or genes at once, or testing in a large scale manner up to entire genomes. While the goal of testing with these broad scope strategies may be increased efficiencies, the outcome of attaining results with no known or unknown clinical utility (variants of uncertain significance) has the potential to cause harm via the uncertainty of the results.[3]

Hearing Loss

Sensorineural hearing loss (SNHL) is hearing loss resulting from damage, disease, or other disorders affecting the inner ear (e.g., cochlea) and/or the auditory nerve (cranial nerve VIII).[4]
This differs from conductive hearing loss that is caused by a problem of the outer or middle ear that interferes with conduction of sound to the inner ear.

Hypopituitarism

Hypopituitarism refers to decreased secretion of pituitary hormones, which can result from diseases of the pituitary gland or from diseases of the hypothalamus.[5] The latter cause diminished secretion of hypothalamic-releasing hormones, thereby reducing secretion of the corresponding pituitary hormone.

Combined Pituitary Hormone Deficiency (CPHD) Panel[6]

Combined pituitary hormone deficiency (CPHD) is a condition characterized by impaired production of growth hormone and at least one of the other 5 hormones produced by the anterior pituitary. The prevalence of CPHD is estimated to be 1 in 8,000 individuals, and approximately 5-30% of cases are familial. affected individuals are ascertained because of a failure to grow and short stature starting in infancy or early childhood. Patients with CPHD are associated with deficiencies of growth hormone (GH), thyroid-stimulating hormone (TSH), gonadotropins (luteinizing hormone (LH) and follicle-stimulating hormone (FSH)), and occasionally adrenocorticotropic hormone (ACTH) (Otto et al. 2015. PubMed ID: 25315032). People with CPHD may have mild hypothyroidism which could cause poor weight gain and fatigue. Other features of CPHD include absent or delayed puberty and incomplete secondary sexual development with infertility, or more complex disorders such as septo-optic dysplasia (SOD) and holoprosencephaly. CPHD is caused by both genetic and nonheritable factors such as trauma, tumor, and infections. Approximately 50-60% of familial CPHD has a genetic basis and pathogenic variants in a number of different genes are found to cause genetically determined CPHD. The genes GLI2, HESX1, LHX3, LHX4, OTX2, POU1F1, PROP1, SOX2, and SOX3 are the most studied ones. Of these, PROP1 pathogenic variants are the most common known cause of this disorder, accounting for approximately 50% of familiar cases, although the incidence in sporadic cases is much lower. These genes all encode transcription factors that are expressed in the developing head, hypothalamus, and/or pituitary, and have been involved in the proper development of the pituitary gland and the specialization of its cell types. Pathogenic variants in these genes perturb ontogenesis of pituitary gonadotropes, somatotropes, lactotropes, and thyrotropes. These developmental defects result in deficiencies of LH, which is needed for normal growth; FSH and GH, which both play a role in sexual development and fertility; TSH, which helps with thyroid gland function; and ACTH, which influences energy production in the body and maintains normal blood sugar and blood pressure levels. CPHD can be inherited in X-linked (SOX3),

autosomal dominant (GLI2, LHX4, HESX1, POU1F1, OTX2, SOX2), or autosomal recessive (HESX1, POU1F1, PROP1, LHX3) manner.

Inherited Peripheral Neuropathies

Targeted Panels

Targeted panel testing for peripheral neuropathies includes panels that are specifically designed to diagnose patients suspected of having an inherited peripheral neuropathy, such as Charcot-Marie-Tooth disease. They may include the following genes: PMP22, MFN2, MPZ, LITAF, and GJB1.

Examples of targeted panels for peripheral neuropathies include, but are not limited to:

- Distal Hereditary Motor Neuropathy Panel (Prevention Genetics)
- Hereditary Neuropathy Panel (GeneDx)
- Invitae Hereditary Sensory and Autonomic Neuropathy Panel (Invitae)
- Invitae Small Fiber Neuropathy Test (Invitae)

Non-Targeted Panels

Some commercially available panels include testing for a large number of disorders that could be distinguished based on clinical presentation. Non-targeted panels for neuropathies and related disorders, but are not limited to:

- Comprehensive Neuropathy Panel (Prevention Genetics)
- Comprehensive Neuropathies (NGS Panel and Copy Number Analysis + mtDNA) (MNG Laboratories)
- Comprehensive Peripheral Neuropathy Gene Panel (Mayo Clinic)
- Invitae Comprehensive Neuropathies Panel (Invitae)

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding genetic testing for specific indications. Below is a summary of the available evidence identified through August 2026.

Hearing Loss

Shearer and colleagues performed a meta-analysis in 2015 focusing on the current genetic tests used to evaluate hearing loss.[7] Twenty studies were included, containing 426 controls and 603 patients with idiopathic hearing loss. Several genetic panels such as OtoGenetics Deafness Test and OtoGenome were used. Overall, the controls showed good sensitivity and specificity (over 99%), and the diagnostic rate was found to be 41% (with a range of 10% – 83%). The authors concluded that "comprehensive genetic testing should form the cornerstone of a tiered approach to clinical evaluation of patients with hearing loss along with history, physical exam, and audiometry and can determine further testing that may be required, if any."

In 2016, Sloan-Heggen and colleagues completed parallel sequencing on 1,119 "sequentially accrued" patients. 440 (39%) of these patients were found to have a genetic etiology for hearing loss.[8] Pathogenic variants were found in 49 genes, and various alterations such as missense variants (49% of the alterations), copy number variants (18%), insertions or deletions (13%), and nonsense variants (8%) were found. The authors noted the wide variety of the genetic spectrum of hearing loss.

Unilateral**:**

In 2016, Sloan-Heggen and colleagues published a retrospective study on comprehensive genetic testing in patients with hearing loss.[8] There were 1119 patients, 69 of which had unilateral hearing loss. Patients with bilateral hearing loss were significantly more likely to receive a diagnosis than patients with asymmetric or unilateral hearing loss (44, 22 and 1 %, respectively; $p < 0.005$).

In 2019 (updated in 2022), Hayes published a clinical utility evaluation on genetic testing in patients with or suspected of prelingual nonsyndromic hearing loss.[9] One study was identified that evaluated the clinical utility of genetic testing in this population, evaluating 209 patients and studying their psychological well-being pre and post testing. Hayes concluded that there was insufficient evidence to evaluate the clinical utility of genetic testing in patients with or suspected of prelingual nonsyndromic hearing loss.

Hypopituitarism

According to Weizmann Institute of Science (MalaCards) and Medline Plus, 9 genes (GLI2, HESX1, LHX3, LHX4, OTX2, POU1F1, PROP1, SOX2, and SOX3 are most commonly associated with CPHD.[10,11]

According to Medline Plus:[11]

"Most cases of combined pituitary hormone deficiency are sporadic, which means they occur in people with no history of the disorder in their family. Less commonly, this condition has been found to run in families. When the disorder is familial, it can have an autosomal dominant or an autosomal recessive pattern of inheritance."

CLINICAL PRACTICE GUIDELINES

Connective Tissue Disorders

American Academy of Pediatrics

In 2023, the American Academy of Pediatrics updated its clinical report focused on health supervision for children with Marfan syndrome. This clinical report notes the following with regard to genetic testing:

- "Younger patients at risk for Marfan syndrome based on clinical features or a positive family history should be evaluated periodically until their growth is complete or preferably undergo appropriate genetic testing."
- "...genetic testing in Marfan syndrome has become an important part of the diagnosis and management of the condition."
- "For those suspected to have Marfan syndrome on clinical grounds after physical, cardiac, and ophthalmic evaluation but who may not meet full clinical criteria, one should consider FBN1 testing"
- "Patients who fit clinical criteria for Marfan syndrome in whom no pathogenic variant is found in the FBN1 gene should continue to be followed according to the health supervision for Marfan syndrome. In addition, broader genomic testing should be considered in these individuals."
- "When a new diagnosis of Marfan syndrome is made in a child or adolescent, both parents and at-risk first-degree relatives should have physical, ophthalmologic, and cardiac evaluations as well as consideration of genetic testing. Similarly, when a new diagnosis of Marfan syndrome is made in a parent, all children should be screened for
  manifestations of Marfan syndrome."
- "Prenatal genetic testing for FBN1 mutations may be helpful to confirm Marfan syndrome as well as reveal specific mutations in FBN1 that may be more typically associated with this severe form and, therefore, reduced survivability."

American College of Medical Genetics and Genomics (ACMG)

The ACMG issued guidelines (2012) on the evaluation of adolescents or adults with some features of Marfan syndrome (MFS). The guidelines recommended the following:

“If there is no family history of MFS, then the subject has the condition under any of the following four situations

- A dilated aortic root (defined as greater than or equal to two standard deviations above the mean for age, sex, and body surface area) and ectopia lentis
- A dilated aortic root and a mutation [pathogenic variant] in FBN1 that is clearly pathologic
- A dilated aortic root and multiple systemic features … or
- Ectopia lentis and a mutation [pathogenic variant] in FBN1 that has previously been associated with aortic disease.”

“If there is a positive family history of MFS (independently ascertained with these criteria), then the subject has the condition under any of the following three situations:

- Ectopia lentis
- Multiple systemic features … or

- A dilated aortic root (if over 20 years, greater than two standard deviations; if younger than 20, greater than three standard deviations)”

The systemic features are weighted by a scoring system.

American College of Cardiology and American Heart Association

Joint evidence-based guidelines (2022) from the American College of Cardiology (ACC) and American Heart Association (AHA) for the diagnosis and management of aortic disease include MFS, Loeys-Dietz syndrome, and Ehlers-Danlos syndrome Genetic testing for thoracic aortic disease (TAD) was addressed in the following guideline statement:

"Genetic testing is recommended for individuals with syndromic features, family history of TAD, and/or early age of disease onset. Thoracic aortic imaging is recommended for first-degree relatives of all individuals with TAD, regardless of age of onset, to detect asymptomatic aneurysms. Positive genetic testing should trigger gene-based management and cascade

testing of at-risk relatives. When testing is negative or reveals variants of unknown significance, first-degree relatives should undergo screening aortic imaging."

Specific recommendations for genetic testing and screening of family members for TAD include the following:

- In patients with aortic root/ascending aortic aneurysms or aortic dissection and risk factors for HTAD, genetic testing to identify pathogenic/likely pathogenic variants (i.e., mutations) is recommended.
- In patients with an established pathogenic or likely pathogenic variant in a gene predisposing to HTAD, it is recommended that genetic counseling be provided and the patient’s clinical management be informed by the specific gene and variant in the gene.
- In patients with TAD who have a pathogenic/likely pathogenic variant, genetic testing of at-risk biological relatives (i.e., cascade testing) is recommended. In family members who are found by genetic screening to have inherited the pathogenic/likely pathogenic variant, aortic imaging with TTE (if aortic root and ascending aorta are adequately visualized, otherwise with CT or MRI) is recommended.
- In a family with aortic root/ascending aortic aneurysms or aortic dissection, if the disease-causing variant is not identified with genetic testing, screening aortic imaging (as per recommendation 4) of at-risk biological relatives (i.e., cascade testing) is recommended.
- In patients with aortic root/ascending aortic aneurysms or aortic dissection, in the absence of either a known family history of TAD or pathogenic/likely pathogenic variant, screening aortic imaging (as per recommendation 4) of first-degree relatives is recommended.

American Heart Association

In 2020, the American Heart Association issued a scientific statement focused on genetic testing and its implications for the management of inherited cardiovascular diseases. Approaches for the evaluation of patients with a confirmed or suspected diagnosis of inherited cardiovascular disease, as well as

individuals with secondary or incidental genetic findings are summarized in the statement. Briefly, the statement notes that:

- Genetic testing typically should be reserved for patients with a confirmed or suspected diagnosis of an inherited cardiovascular disease or for individuals at high a priori risk resulting from a previously identified pathogenic variant in their family.
- Pathogenic and likely pathogenic variants might confirm diagnoses of suspected diseases (ie, serve as major criteria) or warrant changes in clinical management (ie, are actionable) if they occur in certain genes in patients with certain diseases.

Familial Hypercholesterolemia

Molecular genetic status testing is considered part of the diagnostic criteria for familial hypercholesterolemia by multiple clinical practice guidelines.[12-16]

Hearing Loss

UpToDate

In 2022, UpToDate published guidelines on Hearing loss in children: Screening and evaluation.[4] They recommend the following:

"For patients with bilateral SNHL without syndromic findings, comprehensive genetic testing using NGS should be performed as the initial test.

The authors continue to discuss unilateral hearing loss: "For infants and children with bilateral SNHL, the evaluation typically includes comprehensive genetic testing of the patient and possibly other family members. By contrast, the yield of comprehensive genetic testing is low in children with unilateral SNHL in the absence of syndromic findings."

"Unilateral SNHL – For children with unilateral SNHL, we suggest not routinely performing comprehensive genetic testing with NGS to evaluate for nonsyndromic hearing loss. The yield of NGS in this setting is low.

Joint Commission on Infant Hearing (JCIH)

In 2007, the JCIH recommended that evaluation of infants with confirmed hearing loss should include a review of family history of specific genetic disorders or syndromes, including genetic testing for gene mutations such as GJB2 (connexin-26), and syndromes commonly associated with early-onset childhood sensorineural hearing loss.[17] In 2013, a supplement by the ASHA was added to the JCIH. The 2013 supplement also stated that medical providers must "understand atypical development etiologies and diagnoses, and refer for medical-genetic evaluation" and that families must be educated on the "importance of medical, genetic, ophthalmologic, and cardiac (EKG) evaluations on children with any type and degree of hearing loss".

In 2019, the JCIH published an updated position statement.[18] They note that the American College of Medical Genetics and Genomics recommends offering genetic counseling and testing to all infants who

are deaf or hard of hearing and their families. A geneticist's evaluation should include "a review of family history of specific genetic disorders or syndromes, genetic testing for gene mutations such as GJB2 (connexin-26), and syndromes commonly associated with early-onset hearing loss".

International Pediatric Otolaryngology Group (IPOG)

In 2016, the IPOG released their guidelines on hearing loss in the pediatric patient.[19] Concerning which children should be offered comprehensive genetic testing they recommend the following:

"Comprehensive genetic testing should be offered to children with bilateral ANSD, or unilateral ANSD if imaging for cochlear nerve dysplasia is negative and no obvious acquired cause exists."
"After an audiogram, comprehensive genetic testing has the highest diagnostic yield of any single test for bilateral sensorineural hearing loss."
In addressing the question "Should single gene or directed genetic testing be used?", they make the following consensus recommendation statements:
"In the setting of comprehensive genetic testing, single gene testing is of low diagnostic yield and should not be offered as part of an initial workup unless a known family history exists."
"Directed genetic testing for GJB2/GJB6 should be considered if comprehensive genetic testing is unavailable."
"Directed genetic testing may be considered in consultation with a geneticist if comprehensive genetic testing is negative but suspicion for a genetic cause still exists."

American Academy of Pediatrics (AAP)

The AAP also recommends genetic testing for evaluation of hearing loss.[20] Testing protocol typically tests GJB2/6 first, then applies targeted next generation sequencing of gene panels for recessive, dominant, x-linked patterns or syndromic hearing loss (AAP). AAP also notes that it is important to note that genetic testing "cannot identify 100% of genetic hearing loss; negative genetic testing does not rule out a genetic form of hearing loss."

Hypopituitarism

UpToDate

According to UpToDate's 2022 guideline on Causes of Hypopituitarism: genes such as HESX1, LHX3, LHX4, and PROP1 have strong associations with CPHD, both sporadic and familial.[21]

"In addition to pituitary adenomas and their treatment (surgery or radiation therapy), other pituitary causes include… Mutations in genes that encode transcription factors, such as PROP-1, POU1F1, TPIT, HESX1, LHX3, and LHX4, that are important for differentiation of different pituitary cell types and/or pituitary organogenesis."

No clinical guidelines were identified that find genetic testing clinically useful in determining treatment for CPHD and hypopituitarism.

Inherited Peripheral Neuropathies

American Academy of Neurology (AAN)

In 2009 (reaffirmed 2022), the AAN published a clinical practice guideline.[22] Authors recommended a tiered approach for the evaluation of distal symmetric polyneuropathy, and for suspected hereditary neuropathies, which concluded that:

- Genetic testing is established as useful for the accurate diagnosis and classification of hereditary neuropathies (level A classification of recommendations- established as effective, ineffective, or harmful for the given condition in the specified population)
- Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype (level C- possibly effective, ineffective, or harmful for the given condition in the specified population)
- Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features and should focus on the most common abnormalities which are CMT1A duplication/HNPP deletion in PMP22, GJB1 and MFN2 screening
- There is insufficient evidence to determine the usefulness of routine genetic testing in patients with cryptogenic polyneuropathy who do not exhibit a hereditary neuropathy phenotype (level U-data inadequate or conflicting; given current knowledge).

American Academy of Family Physicians (AAFP)

In 2020, the AAFP published guidelines addressing evaluation and differential diagnosis of peripheral neuropathy.[23] Authors recommended genetic testing in a patient with suspected peripheral neuropathy if basic blood tests are negative, electrodiagnostic studies suggest an axonal etiology, and diseases such as diabetes, toxic medications, thyroid disease, and vasculitis can be ruled out.

Macrocephaly and Overgrowth Genetic Testing

Clinical practice guidelines suggest that genetic testing for macrocephaly and overgrowth is advised when unexplained large head size, developmental delays, abnormal physical features, or a family history of similar conditions are present. It assists in diagnosing underlying syndromes, managing risks, and guiding treatment.[24,25]

EVIDENCE SUMMARY

Connective Tissue Disorders

Genetic testing for connective tissue disorders, such as Marfan syndrome (MFS), is crucial when clinical features, family history, or risk factors are present. Testing is advised for younger patients at risk, individuals with incomplete clinical criteria, and those with family histories, aiding diagnosis and management. When clinical criteria are met but no pathogenic variant is found, broader genomic testing is suggested. For new MFS diagnoses in children or parents, genetic testing and evaluations for first-degree relatives are recommended. In cases of thoracic aortic disease (TAD), genetic testing is recommended for those with syndromic features or early onset, guiding gene-based management and cascade testing of relatives. Testing should confirm suspected inherited cardiovascular diseases, with pathogenic variants prompting changes in clinical management. Additionally, genetic testing helps establish diagnoses for hereditary disorders, though variants of uncertain significance require careful

contextual consideration. Thus, genetic testing is medically necessary for accurate diagnosis, effective management, and preventive care in connective tissue disorders.

Familial Hypercholesterolemia

Clinical guidelines recommend genetic testing for familial hypercholesterolemia (FH) to allow for precise diagnosis and early intervention, which is critical for managing cholesterol levels, initiating appropriate treatments, and reducing the risk of heart disease.

Hearing Loss

While studies continue to be elusive regarding specific information on comprehensive gene testing, several clinical practice guidelines continue to support this testing, particularly in patients with bilateral nonsyndromic hearing loss. There remains some conflicting reports regarding if comprehensive genetic testing should be completed during the initial test vs after single gene testing. However, the majority of the clinical practice guidelines support the comprehensive testing initially. The ACMG guideline which indicated single gene mutations should be considered first did indicate that comprehensive testing may be more cost effective. Testing for unilateral hearing loss is not recommended due to probable causes being frequently being structural in nature.

There is insufficient evidence to show that genetic panels have diagnostic utility for children with nonsyndromic unilateral hearing loss. Few studies were conducted on genetic testing for unilateral hearing loss, and the limited data available suggests that large genetic panels have little diagnostic yield. Furthermore, clinical practice guidelines advise against the use of genetic panels for diagnosing unilateral hearing loss in nonsyndromic patients. Therefore, multi-gene genetic panel testing is considered not medically necessary in patients with nonsyndromic unilateral hearing loss.

Macrocephaly and Overgrowth

Genetic testing for macrocephaly and overgrowth allows early diagnosis which enables tailored medical management, proactive surveillance for associated risks like tumor development, and appropriate intervention strategies.

Hypopituitarism

Familial CPHD is uncommon, but it may affect family planning. Moreover, management requires a multi-disciplinary team approach to ensure adequacy of hormone replacement and evaluation of evolving hormone deficiencies. Genetic counselling should be offered to parents in whose infant a genetic cause has been identified. Therefore, genetic testing for CPHD in patients with hypopituitarism has some clinical utility and may be considered medically necessary.

Inherited Peripheral Neuropathies

Evidence is sufficient to support the use of genetic testing for individuals who display signs and symptoms of an inherited peripheral neuropathy.[26-28] This is particularly beneficial for individuals who

cannot receive a clinical diagnosis and those who need a genetic diagnosis to make informed decisions about reproduction.

HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) defines health equity as the state in which everyone has a fair and just opportunity to attain their highest level of health. Achieving health equity requires addressing health disparities and social determinants of health. A health disparity is the occurrence of diseases at greater levels among certain population groups more than among others. Health disparities are linked to social determinants of health which are non-medical factors that influence health outcomes such as the conditions in which people are born, grow, work, live, age, and the wider set of forces and systems shaping the conditions of daily life. Social determinants of health include unequal access to health care, lack of education, poverty, stigma, and racism.

The U.S. Department of Health and Human Services Office of Minority Health calls out unique areas where health disparities are noted based on race and ethnicity. Providence Health Plan (PHP) regularly reviews these areas of opportunity to see if any changes can be made to our medical or pharmacy policies to support our members obtaining their highest level of health. Upon review, PHP creates a Coverage Recommendation (CORE) form detailing which groups are impacted by the disparity, the research surrounding the disparity, and recommendations from professional organizations. PHP Health Equity COREs are updated regularly and can be found online here.

BILLING GUIDELINES AND CODING

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).

CODES*		
CPT	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
	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
	0355U	APOL1 (apolipoprotein L1) (eg, chronic kidney disease), risk variants (G1, G2)
	0604U	Allergy and immunology (chronic recurrent angioedema), 4 bradykinin peptides, liquid chromatography and tandem mass spectrometry (LC-MS/ MS), whole blood, quantitative
	0605U	Allergy and immunology (hereditary alpha tryptasemia), DNA, analysis of TPSAB1 gene copy number variation using digital PCR, whole blood, results reported with genotype-specific interpretation of alpha-tryptase copy number and algorithmic classification as normal or abnormal
	0613U	Oncology (urothelial carcinoma), DNA methylation and mutation analysis of 6 biomarkers (TWIST1, OTX1, ONECUT2, FGFR3, HRAS, TERT promoter region), methylation-specific PCR and targeted next-generation sequencing, urine, algorithm reported as a probability index for bladder cancer and upper tract urothelial carcinoma
	0628U	Nephrology (kidney disease-related genetic conditions), genomic analysis, renal disease panel, saliva, DNA, next-generation sequencing of 449 genes, reported as pathogenic or likely pathogenic variants of uncertain significance or risk alleles
	0679U	Oncology (hereditary hematologic cancer), genomic DNA, whole genome sequence (single-nucleotide variants, deletions/insertions, and characterized intronic variants), copy number variants, duplications/deletions, mobile element insertions and inversions, analysis of over 105 genes, genomic DNA isolated from blood, saliva, cultured skin fibroblasts (skin biopsy), identification and categorization of genetic variants
	0696U	Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin-embedded (FFPE) tumor tissue, RNA analysis, 350 or more genes for RNA alterations (eg, gene rearrangements and splice isoforms)

	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)
	81120	IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)
	81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)
	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 (ALF transcription elongation factor 2 [FMR2]) (eg, fragile X intellectual disability 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81172	AFF2 (ALF transcription elongation factor 2 [FMR2]) (eg, fragile X intellectual disability 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
	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)
	81200	ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g., E285A, Y231X)
	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)
	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
	81219	CALR (calreticulin)(eg myeloproliferative disorders, gene analysis, common variants in exon 9)
	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
	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)
	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)
	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 messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81244	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
	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)
	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)
	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
	81260	IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex- associated protein)(e.g. familial dysautonomia) gene analysis, common variants
	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
	81274	HTT (huntingtin) (eg, Huntington disease) gene analysis; characterization of alleles (eg, expanded size)
	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)
	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)
	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
	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)
	81312	PABPN1 (poly[A] binding protein nuclear 1) (eg, oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
	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

	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
	81330	SMPD1 (sphingomyelin phosphodiesterase 1, acid lysomal) (e.g., Niemann-Pick disease Type A) gene analysis, common variants (e.g., R496L, L302P, fsP330)
	81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and Ubiquitin protein ligase E3A) (e.g., Prader-Willi syndrome and/or Angelman syndrome methylation analysis
	81332	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)
	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)

	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
	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)
	81410	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
	81411	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1
	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
	81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence 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-related disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
	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)
	81441	Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2,

		RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2
	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
	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)
	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)
	81479	Unlisted Molecular Pathology
	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
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	S3870	Comparative genomic hybridization (cgh) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
6/2023	Removed PA requirement for CPT 81256. Removed CPT 0049U to be placed on "Genetic Testing: Myeloproliferative Diseases" policy.
7/2023	Changed denial for criterion III. to "not medically necessary,"
11/2023	Annual review. Expanded criteria to include specific tests with additional criteria.
1/2024	Q1 2024 code set update. Code description revisions.
4/2024	Interim update. Added criteria addressing inherited peripheral neuropathies.
12/2024	Annual update. Additional criteria added to "specific indications."
1/2025	Q1 2025 code set update. Revised and expired codes.
1/2026	Annual update. Added criteria for connective tissue disorders. Added 2 codes. Q1 2026 code set update.
4/2026	Q2 code set update.

10/2026	Q3 2026 code set update.
11/2026	Annual update. No changes to codes or criteria.