



Louisiana

Genetic Testing for the Diagnosis of inherited Peripheral Neuropathies

Policy # 00378

Original Effective Date: 08/21/2013

Current Effective Date: 05/10/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing when the diagnosis of an inherited peripheral motor or sensory neuropathy is suspected due to signs and/or symptoms but a definitive diagnosis cannot be made to be **eligible for coverage.****

Patient Selection Criteria:

Coverage eligibility will be considered in individuals when the following criteria are met:

- Patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype may be considered for initial genetic testing of the most common genetic abnormalities, e.g. PMP22 (CMT1A duplication/ deletion), GJB1, or MFN2. Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features. If these initial tests are negative, then second bullet will be considered.
- Evaluation of rarer genetic causes would be appropriate only if initial testing is negative.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

The use of genetic testing when the diagnosis of an inherited peripheral motor or sensory neuropathy is suspected due to signs and/or symptoms but a definitive diagnosis cannot be made when patient selection criteria are not met is considered to be **investigational.***

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Based on review of available data, the Company considers genetic testing for an inherited peripheral motor or sensory neuropathy for all other indications to be **investigational**.*

Based on review of available data, the Company considers initial testing with comprehensive multigene panels that test most known genes related to hereditary neuropathies to be **investigational**.*

Policy Guidelines

This policy addresses the hereditary motor and sensory peripheral neuropathies, of which peripheral neuropathy is the primary clinical manifestation. A number of other hereditary disorders may have neuropathy as an associated finding but typically have other central nervous system and occasional other systemic findings. Examples include Refsum disease, various lysosomal storage diseases, and mitochondrial disorders.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

Inherited Peripheral Neuropathies

Inherited peripheral neuropathies are a clinically and genetically heterogeneous group of disorders. The estimated prevalence in aggregate is 1 in 2500 persons, making inherited peripheral neuropathies the most common inherited neuromuscular disease.

Peripheral neuropathies can be subdivided into two major categories: primary axonopathies and primary myelinopathies, depending on which portion of the nerve fiber is affected. The further

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anatomic classification includes fiber type (eg, motor vs sensory, large vs small) and gross distribution of the nerves affected (eg, symmetry, length-dependency).

Inherited peripheral neuropathies are divided into the hereditary motor and sensory neuropathies, hereditary neuropathy with liability to pressure palsies (HNPP), and other miscellaneous, rare types (eg, hereditary brachial plexopathy, hereditary sensory, autonomic neuropathies). Other hereditary metabolic disorders, such as Friedreich ataxia, Refsum disease, and Krabbe disease, may be associated with motor and/or sensory neuropathies but typically have other predominating symptoms. This evidence review focuses on the hereditary motor and sensory neuropathies and HNPP.

A genetic etiology of peripheral neuropathy is typically suggested by generalized polyneuropathy, family history, lack of positive sensory symptoms, early age of onset, symmetry, associated skeletal abnormalities, and very slowly progressive clinical course. A family history of at least three generations with details on health issues, the cause of death, and age at death should be collected.

Charcot-Marie-Tooth Disease

Hereditary Motor and Sensory Neuropathies

Most inherited polyneuropathies were originally described clinically as variants of CMT disease. The clinical phenotype of CMT is highly variable, ranging from minimal neurologic findings to the classic picture with pes cavus and “stork legs” to a severe polyneuropathy with respiratory failure. CMT disease is genetically and clinically heterogeneous. Variants in more than 30 genes and more than 44 different genetic loci have been associated with the inherited neuropathies. Also, different pathogenic variants in a single gene can lead to different inherited neuropathy phenotypes and inheritance patterns. A 2016 cross-sectional study of 520 children and adolescents with CMT found variability in CMT-related symptoms across the 5 most commonly represented subtypes.

CMT subtypes are characterized by variants in one of several myelin genes, which lead to abnormalities in myelin structure, function, or upkeep. There are seven subtypes of CMT, with type 1 and 2 representing the most common hereditary peripheral neuropathies.

Most cases of CMT are autosomal dominant, although autosomal recessive and X-linked dominant forms exist. Most cases are CMT type 1 (approximately 40%-50% of all CMT cases, with 78%-80%

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of those due to *PMP22* variants). CMT type 2 is associated with 10% to 15% of CMT cases, with 20% of those due to *MFN2* variants.

A summary of the molecular genetics of CMT is outlined in Table 1.

Table 1. Molecular Genetics of CMT Variants

| Locus | Gene | Protein Product | Prevalence (if known) |
|------------|--------------|---|-----------------------|
| CMT type 1 | | | |
| CMT1A | <i>PMP22</i> | Peripheral myelin protein 22 | 70%-80% of CMT1 |
| CMT1B | <i>MPZ</i> | Myelin P0 protein | 10%-12% of CMT1 |
| CMT1C | <i>LITAF</i> | Lipopolysaccharide-induced tumor necrosis factor- α factor | \approx 1% of CMT1 |
| CMT1D | <i>EGR2</i> | Early growth response protein 2 | |
| CMT1E | <i>PMP22</i> | Peripheral myelin protein 22 (sequence changes) | \approx 1% of CMT1 |
| CMT1F/2E | <i>NEFL</i> | Neurofilament light polypeptide | |
| CMT type 2 | | | |
| CMT2A1 | <i>KIF1B</i> | Kinesin-like protein KIF1B | |
| CMT2A2 | <i>MFN2</i> | Mitofusin-2 | 20% of CMT2 |
| CMT2B | <i>RAB7A</i> | Ras-related protein Rab-7 | |
| CMT2B1 | <i>LMNA</i> | Lamin A/C | |
| CMT2B2 | <i>MED25</i> | Mediator of RNA polymerase II transcription subunit 25 | |
| CMT2C | <i>TRPV4</i> | Transient receptor potential cation channel subfamily V member 4 | |
| CMT2D | <i>GARS</i> | Glycyl-tRNA synthetase | |
| CMT2E/1F | <i>NEFL</i> | Neurofilament light polypeptide | |
| CMT2F | <i>HSPB1</i> | Heat-shock protein beta-1 | |
| CMT2G | 12q12-q13 | Unknown | |
| CMT2H/2K | <i>GDAP1</i> | Ganglioside-induced differentiation-associated protein 1 | |

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| Locus | Gene | Protein Product | Prevalence (if known) |
|--------------|----------------|---|-----------------------|
| CMT2I/2J | <i>MPZ</i> | Myelin P0 protein | |
| CMT2L | <i>HSPB8</i> | Heat-shock protein beta-8 | |
| CMT2N | <i>AARS</i> | Alanyl-tRNA synthetase, cytoplasmic | |
| CMT2O | <i>DYNC1H1</i> | Cytoplasmic dynein 1 heavy chain 1 | |
| CMT2P | <i>LRSAM1</i> | E3 ubiquitin-protein ligase LRSAM1 | |
| CMT2S | <i>IGHMBP2</i> | DNA-binding protein SMUBP-2 | |
| CMT2T | <i>DNAJB2</i> | DnaJ homolog subfamily B member 2 | |
| CMT2U | <i>MARS</i> | Methionine-tRNA ligase, cytoplasmic | |
| CMT type 4 | | | |
| CMT4A | <i>GDAP1</i> | Ganglioside-induced differentiation-associated protein 1 | |
| CMT4B1 | <i>MTMR2</i> | Myotubularin-related protein 2 | |
| CMT4B2 | <i>SBF2</i> | Myotubularin-related protein 13 | |
| CMT4C | <i>SH3TC2</i> | SH3 domain and tetratricopeptide repeats-containing protein 2 | |
| CMT4D | <i>NDRG1</i> | Protein NDRG1 | |
| CMT4E | <i>EGR2</i> | Early growth response protein 2 | |
| CMT4F | <i>PRX</i> | Periaxin | |
| CMT4H | <i>FGD4</i> | FYVE, RhoGEF and PH domain-containing protein 4 | |
| CMT4J | <i>FIG4</i> | Phosphatidylinositol 3, 5-biphosphate | |
| X-linked CMT | | | |
| CMTX1 | <i>GJB1</i> | Gap junction beta-1 protein (connexin 32) | 90% of X-linked CMT |
| CMTX2 | <i>Xp22.2</i> | Unknown | |
| CMTX3 | <i>Xq26</i> | Unknown | |
| CMTX4 | <i>AIFM1</i> | Apoptosis-inducing factor 1 | |
| CMTX5 | <i>PRPS1</i> | Ribose-phosphate pyrophosphokinase 1 | |
| CMTX6 | <i>PDK3</i> | Pyruvate dehydrogenase kinase isoform 3 | |

Adapted from Bird (2016).

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CMT: Charcot-Marie-Tooth.

The clinical features of CMT are briefly summarized.

CMT Type 1

CMT1 is an autosomal dominant, demyelinating peripheral neuropathy characterized by distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity. It is usually slowly progressive and often associated with pes cavus foot deformity, bilateral foot drop, and palpably enlarged nerves, especially the ulnar nerve at the olecranon groove and the greater auricular nerve. Affected people usually become symptomatic between ages 5 and 25 years, and lifespan is not shortened. Less than 5% of people become wheelchair-dependent. CMT1 is inherited in an autosomal dominant manner. The CMT1 subtypes (CMT 1A-E) are separated by molecular findings and are often clinically indistinguishable. CMT1A accounts for 70% to 80% of all CMT1, and about two-thirds of probands with CMT1A have inherited the disease-causing variant, and about one-third have CMT1A as the result of a de novo variant.

CMT1A involves duplication of the *PMP22* gene. *PMP22* encodes an integral membrane protein, peripheral membrane protein 22, which is a major component of myelin in the peripheral nervous system. The phenotypes associated with this disease arise because of abnormal *PMP22* gene dosage effects. Two normal alleles represent the normal wild-type condition. Four normal alleles (as in the homozygous CMT1A duplication) result in the most severe phenotype, whereas three normal alleles (as in the heterozygous CMT1A duplication) cause a less severe phenotype.

CMT Type 2

CMT2 is a non-demyelinating (axonal) peripheral neuropathy characterized by distal muscle weakness and atrophy, mild sensory loss, and normal or near-normal nerve conduction velocities. Clinically, CMT2 is similar to CMT1, although typically less severe. The subtypes of CMT2 are similar clinically and distinguished only by molecular genetic findings. CMT2B1, CMT2B2, and CMT2H/K are inherited in an autosomal recessive manner; all other subtypes of CMT2 are inherited in an autosomal dominant manner. The most common subtype of CMT2 is CMT2A, which accounts for approximately 20% of CMT2 cases and is associated with variants in the *MFN2* gene.

X-Linked CMT

CMT X type 1 is characterized by a moderate-to-severe motor and sensory neuropathy in affected males and mild to no symptoms in carrier females. Sensorineural deafness and central nervous

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system symptoms also occur in some families. CMT X type 1 is inherited in an X-linked dominant manner. Molecular genetic testing of *GJB1* (Cx32), which is available on a clinical basis, detects about 90% of cases of CMT X type 1.

CMT Type 4

CMT type 4 is a form of hereditary motor and sensory neuropathy that is inherited in an autosomal recessive fashion and occurs secondary to myelinopathy or axonopathy. It occurs more rarely than the other forms of CMT neuropathy, but some forms may be rapidly progressive and/or associated with severe weakness.

Hereditary Neuropathy with Liability to Pressure Palsies

The largest proportion of CMT1 cases are due to variants in *PMP22*. In HNPP (also called tomaculous neuropathy), inadequate production of *PMP22* causes nerves to be more susceptible to trauma or minor compression or entrapment. HNPP patients rarely present symptoms before the second or third decade of life. However, some have reported presentation as early as birth or as late as the seventh decade of life. The prevalence is estimated at 16 persons per 100000, although some authors have indicated a potential for under diagnosis of the disease. An estimated 50% of carriers are asymptomatic and do not display abnormal neurologic findings on clinical examination. HNPP is characterized by repeated focal pressure neuropathies such as carpal tunnel syndrome and peroneal palsy with foot drop and episodes of numbness, muscular weakness, atrophy, and palsies due to minor compression or trauma to the peripheral nerves. The disease is benign with complete recovery occurring within a period of days to months in most cases, although an estimated 15% of patients have residual weakness following an episode. Poor recovery usually involves a history of prolonged pressure on a nerve, but, in these cases, the remaining symptoms are typically mild.

PMP22 is the only gene for which a variant is known to cause HNPP. A large deletion occurs in approximately 80% of patients, and the remaining 20% of patients have single nucleotide variants (SNVs) and small deletions in the *PMP22* gene. One normal allele (due to a 17p11.2 deletion) results in HNPP and a mild phenotype. SNVs in *PMP22* have been associated with a variable spectrum of HNPP phenotypes ranging from mild symptoms to representing a more severe, CMT1-like syndrome. Studies have also reported that the SNV frequency may vary considerably by ethnicity. About 10% to 15% of variant carriers remain clinically asymptomatic, suggesting incomplete penetrance.

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Treatment

Currently, there is no therapy to slow the progression of neuropathy for the inherited peripheral neuropathies. A 2015 systematic review of exercise therapies for CMT including 9 studies described in 11 articles reported significant improvements with functional activities and physiological adaptations with exercise. Supportive treatment, if necessary, is generally provided by a multidisciplinary team including neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Treatment choices are limited to physical therapy, use of orthotics, surgical treatment for skeletal or soft tissue abnormalities, and drug treatment for pain. Avoidance of obesity and drugs associated with nerve damage (eg, vincristine, paclitaxel, cisplatin, isoniazid, nitrofurantoin) is recommended in CMT patients.

Supportive treatment for HNPP can include transient bracing (eg, wrist splint or ankle-foot orthosis), which may become permanent in some cases of foot drop. Prevention of HNPP manifestations can be accomplished by wearing protective padding (eg, elbow or knee pads) to prevent trauma to nerves during activity. Some have reported that vincristine should also be avoided in HNPP patients. Ascorbic acid has been investigated as a treatment for CMT1A based on animal models, but a 2013 trial in humans did not demonstrate significant clinical benefit. Attarian et al (2014) reported results of an exploratory phase 2 randomized, double-blind, placebo-controlled trial of PXT3003, a low-dose combination of 3 approved compounds (baclofen, naltrexone, sorbitol) in 80 adults with CMT1A. The trial demonstrated the safety and tolerability of the drug. Mandel et al (2015) included this randomized controlled trial and 3 other trials (1 of ascorbic acid, 2 of PXT3003) in a meta-analysis.

Molecular Genetic Testing

Multiple laboratories offer individual variant testing for genes involved in hereditary sensory and motor neuropathies, which would typically involve sequencing analysis via Sanger sequencing or next-generation sequencing followed by deletion/duplication analysis (ie, with array comparative genomic hybridization) to detect large deletions or duplications. For the detection of variants in *MFN2*, whole gene or select exome sequence analysis is typically used to identify SNVs, in addition to or followed by deletion or duplication analysis for the detection of large deletions or duplications.

A number of genetic panel tests for the assessment of peripheral neuropathies are commercially available. For example, GeneDx (Gaithersburg, MD) offers an Axonal CMT panel, which uses next-

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generation sequencing and exon array comparative genomic hybridization. The genes tested include: *AARS*, *BSCL2*, *DNM2*, *DYNC1H1*, *GARS*, *GDAP1*, *GJB1*, *HSPB1*, *HSPB8*, *LMNA*, *LRSA*, *MI*, *MED25*, *MFN2*, *MPZ*, *NEFL*, *PRPS1*, *RAB7A*, and *TRPV4*. InterGenetics (Athens, Greece) offers a next-generation sequencing panel for neuropathy that includes 42 genes involved in CMT, along with other hereditary neuropathies. Fulgent Clinical Diagnostics Lab offers a broader NGS panel for CMT that includes 48 genes associated with CMT and other neuropathies and myopathies.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

Rationale/Source

The inherited peripheral neuropathies are a heterogeneous group of diseases that may be inherited in an autosomal dominant, autosomal recessive, or X-linked dominant manner. These diseases can generally be diagnosed based on clinical presentation, nerve conduction studies, and family history. Genetic testing has been used to diagnose specific inherited peripheral neuropathies.

For individuals with suspected inherited motor and sensory peripheral neuropathy who receive testing for genes associated with inherited peripheral neuropathies, the evidence includes case-control and genome-wide association studies. The relevant outcomes are test validity, symptoms, and change in disease status. For the evaluation of hereditary motor and sensory peripheral neuropathies and hereditary neuropathy with liability to pressure palsies, the diagnostic testing yield is likely to be high, particularly when sequential testing is used based on patient phenotype. However, the clinical utility of genetic testing to confirm a diagnosis in a patient with a clinical diagnosis of an inherited peripheral neuropathy is unknown. No direct evidence for improved outcomes with the use of genetic testing for hereditary motor and sensory peripheral neuropathies and hereditary neuropathy with liability to pressure palsies was identified. However, a chain of

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evidence supports the use of genetic testing to establish a diagnosis in cases of suspected inherited motor or sensory neuropathy, when a diagnosis cannot be made by other methods, to initiate supportive therapies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

American Academy of Neurology et al

The American Academy of Neurology and 2 other specialty societies (2009) published an evidence-based, tiered approach for the evaluation of distal symmetric polyneuropathy and suspected hereditary neuropathies, which concluded the following (see Table 2).

Table 2. Recommendations on Distal Symmetric Polyneuropathy and Suspected Hereditary Neuropathies

| Recommendation | LOE ^a |
|--|------------------|
| “Genetic testing is established as useful for the accurate diagnosis and classification of hereditary neuropathies” | A |
| “Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype” | C |
| “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, Cx32 (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” | U |

LOE: level of evidence.

^a Grade A: established as effective, ineffective, or harmful for the given condition in the specified population; grade C: possibly effective, ineffective, or harmful for the given condition in the specified population; grade U: data inadequate or conflicting; given current knowledge.

The American Academy of Neurology website indicates the recommendations were reaffirmed in 2013 and in November 2017 indicated an update is in progress.

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American Academy of Family Physicians

The American Academy of Family Physicians (2010) recommended genetic testing for 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 vasculitides can be ruled out.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|-------------|--|--------------------|-----------------|
| Ongoing | | | |
| NCT01193075 | Natural History Evaluation of Charcot Marie Tooth Disease (CMT) Type (CMT1B), 2A (CMT2A), 4A (CMT4A), 4C (CMT4C), and Others | 5000 | Dec 2019 |
| NCT01193088 | Genetics of Charcot Marie Tooth Disease (CMT) - Modifiers of CMT1A, New Causes of CMT | 1050 | Dec 2019 |

NCT: national clinical trial.

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1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, “Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies”, 2.04.89, February, 2021.

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|------------|--|
| 08/01/2013 | Medical Policy Committee review |
| 08/21/2013 | Medical Policy Implementation Committee approval. New policy. |
| 08/07/2014 | Medical Policy Committee review |
| 08/20/2014 | Medical Policy Implementation Committee approval. No change to coverage. |
| 08/06/2015 | Medical Policy Committee review |
| 08/19/2015 | Medical Policy Implementation Committee approval. No change to coverage. |
| 08/04/2016 | Medical Policy Committee review |
| 08/17/2016 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |

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04/06/2017 Medical Policy Committee review
04/19/2017 Medical Policy Implementation Committee approval. Coverage eligibility statements rewritten.
01/01/2018 Coding update
04/05/2018 Medical Policy Committee review
04/18/2018 Medical Policy Implementation Committee approval. No change to coverage.
04/04/2019 Medical Policy Committee review
04/24/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/02/2020 Medical Policy Committee review
04/08/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2021 Medical Policy Committee review
04/14/2021 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 04/2022

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code |
|------------------|---|
| CPT | 81324, 81325, 81326, 81403, 81404, 81405, 81406, 81448, 81479 |
| HCPCS | No codes |
| ICD-10 Diagnosis | Z31.430, Z31.440 |

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

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****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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