“What’s New” Medical Policy Updates September 2023

Listed below are the recent changes made to policies within the Geisinger Health Plan Medical Policy Portfolio during the month of August that will become **effective October 15, 2023** (unless otherwise specified). The Plan uses medical policies as guidelines for coverage decisions made within members written benefit documents. Coverage may vary by line of business and providers and members are encouraged to verify benefit questions regarding eligibility before applying the terms of the policy.

MP246 Multigene Expression Assay for predicting Recurrence in Colon Cancer – (Revised) – Revised Description; Add Commercial Header

DESCRIPTION:
In early -stage disease, residual circulating tumor DNA (ctDNA) is released from cancer cells, after definitive local therapy and, is indicative of molecular residual disease (MRD). The presence of MRD can be used to identify patients at highest risk of recurrent or metastatic disease. In turn, individuals with no identifiable MRD may be candidates for de-escalation approaches, given the associated favorable prognosis.

Oncotype DX® Colon Cancer Test is a 12-gene expression test designed to predict the likelihood of disease recurrence for stage II colon cancer patients following surgery. Gene expression is quantified from microdissected fixed paraffin-embedded primary colon cancer tissue. The level of expression of the prognosis and predictive signature are then reported as a recurrence score.

Signatera is a personalized molecular residual disease assay (MRD) using circulating tumor DNA (ctDNA), ~~custom~~ paired with a matched normal tissue sample that is designed ~~for each patient to help~~ to identify relapse of disease. The Signatera test is ~~personalized and~~ tumor-informed and filters CHIP-related variants to be filtered out to decrease the rate of false positive findings~~, tailored to fit the unique signature of clonal mutations found in that individual's tumor.~~ Signatera can also be used for longitudinal disease monitoring; please reference MP360 “Minimal Residual Disease NGS Testing”.

INDICATIONS: Requires Prior Medical Director or designee Authorization

For the Commercial Business Segments

The Plan considers Oncotype DX™colon assay or Signatera as medically necessary to assess the need for adjuvant chemotherapy in newly diagnosed colon cancer when ALL of the following are met:

MP267 Amniotic Membrane Transplantation – (Revised) – Add Indications

INDICATIONS:
Preserved human amniotic membrane transplantation may be considered medically necessary for the treatment of ocular surface defects including, but not limited to:

- Bullous keratopathy
- Chemical or thermal burns to ocular surface
- Corneal ulcerations
- Pterygium (either primary and/or recurrent)
- Stevens-Johnson syndrome
- Limbal cell deficiency
- Persistent epithelial defects
- Conjuctival surface reconstruction
- Refractory severe dry eye (DEWS* 3 or 4) with ocular surface damage

- Herpes zoster ophthalmicus

*Note: Dry eye severity level (DEWS) 3 to 4 is assessed based on the following 9 domains:

- Discomfort, severity, and frequency - Severe frequent or constant
- Visual symptoms - chronic and/or constant, limiting to disabling
- Conjunctival Injection - +/- or +/+
- Conjunctive Staining - moderate to marked
- Corneal Staining - marked central or severe punctate erosions
- Corneal/tear signs - Filamentary keratitis, mucus clumping, increase in tear debris
- Lid/meibomian glands - Frequent
- Tear film breakup time - < 5
- Schirmer score (mm/5 min) - < 5

MP273 Gene-based Testing and/or Protein Biomarkers – (Revised) – Add ExoDx Indications

ExoDx Prostate (IntelliScore)

1. The member is age > 50 years of age; and
2. The test will be performed prior to an initial prostate biopsy; or
3. The individual has had a prior negative prostate biopsy; and
4. There is continued clinical suspicion of prostate cancer based on elevation of prostate specific antigen (PSA) >3 ng/mL, and for whom an initial prostate biopsy or repeat prostate biopsy would be recommended by a urologist based on current standard of care.

MP304 Genetic Testing for Inherited Cardiomyopathies and Channelopathies – (Revised) – Extensive Revisions

DESCRIPTION: Risk for structural heart disease and arrhythmia can run in families**.** Cardiomyopathies are diseases of the heart muscle and include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, restrictive cardiomyopathy (RCM), left ventricular noncompaction (LVNC), arrhythmogenic right ventricular cardiomyopathy (ARVC). HCM is a common genetic heart disease reported in pan-ethnic populations. Among patients with HCM, 30% to 60% have an genetic etiology. There are 8 genes associated with HCM with a strong degree of evidence supporting association. Around 30% of patients with DCM are thought to have a hereditary cause for disease. 10-60% of cases with restrictive cardiomyopathy will have an underlying genetic etiology, and the genes responsible for this condition share significant overlap with HCM and DCM.

ARVC and CPVT, while rare, have a high likelihood of a genetic etiology. Among patients with ARVC and CPVT, current evidence suggests up to 66% and 75% of cases, respectively, will have an identifiable genetic variant

Cardiac channelopathies, also called arrythmias, are disorders involving cardiac cells membranes that allow passage of specific ions. These pathways regulate the flow of ions through the cells and are necessary to conduct electrical impulses across the heart. Cardiac channelopathies include long QT syndrome (LQTS), Brugada syndrome (BrS) (also referred to as sudden unexpected nocturnal death syndrome), short QT syndrome (SQTS) and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). Cardiac channelopathies are characterized by delayed repolarization of the myocardium and QT interval alteration, resulting in increased risk for syncope, seizures, and sudden cardiac death (SCD) in the setting of a structurally normal heart and otherwise healthy individual.

Among patients with long QT syndrome 75-80% have a genetic etiology. In short QT syndrome, up to 20% have a genetic etiology. Brugada syndrome can be caused by pathogenic or likely pathogenic variants in SCN5A in 30% of cases, and there are at least 40 other genes associated with the disease that account for <1% of causes. CPVT is rare, and there are two known genes involving this syndrome: RYR2, CASQ2.

Multi-gene panel testing is the most cost-effective and accurate approach to characterize familial cardiomyopathy and channelopathies (arrythmia) because there is considerable phenotypic overlap among these disorders. Therapeutic interventions may be tailored based on genetic findings. The value of genetic testing among individuals with risk for cardiomyopathy is threefold: to understand disease prognosis, to facilitate identification and subsequent screening recommendations for at-risk relatives, and to guide therapeutic options (eg: transthyretin amyloidosis, experimental treatments, need for ICD placement).

Disease-specific panels may change from year to year based on available evidence and technological advancements Test methodology should include sequencing and full deletion and duplication analysis (i.e., detection of large genomic rearrangements) with a benefit of once per lifetime, dependent upon advances in testing technology.

INDICATIONS: When ordered by a cardiologist/electrophysiologist, medical geneticist, or board-certified and licensed (where required) genetic counselor, the following tests including multigene panels are considered to be medically necessary in ANY of the following scenarios :

Channelopathies (Arrhythmias)

The member has a personal history of ANY of the following clinical features or diagnoses:

One or more signs or symptoms of LQTS, SQTS, CPVT, or Brugada, AND a definitive diagnosis cannot be made without genetic testing:

1. Prolonged QT/QTc interval on resting electrocardiogram of >470 msec in males or >480 msec in females without additional risk factors (eg: heart failure, bradycardia, electrolyte imbalance, recent history of QT prolonging drugs); or
1. Short QT/QTc interval of <350 msec; or
2. EKG pattern suggestive of Brugada with or without additional symptoms; or
3. Schwartz score of 2-3 or greater+ (see below); or
4. History of aborted sudden cardiac arrest.
5. History of isolated cardiac conduction disease or with concomitant structural heart disease or extracardiac disease when there is an early age of dx or a suspicion of laminopathy.

The member has a family history of ANY of the following:

1. One first- or second- degree relative with a known history of sudden cardiac arrest or death
2. Two or more relatives on the same side of the family with history sudden cardiac arrest or death
3. A first, second, or third degree relative with a known mutation in an LQTS, SQTS, CPVT, Brugada, or channelopathy gene for which medical management may impact the member's ongoing cardiac surveillance.
4. Two or more first, second, or third degree relatives with a reported clinical history of LQTS, SQTS, CPVT, Brugada, or hereditary arrhythmia but genetic testing may have not been completed or the report is unavailable to direct testing.

~~Long QT Syndrome~~

~~Genetic testing in patients with suspected congenital long QT syndrome (LQTS) may be considered medically necessary for the following indications:~~

~~Individuals who do not meet the clinical criteria for LQTS (i.e., Schwartz score* less than 4), but who have any of the following:~~

- ~~a first, second, or third-degree relative with a known LQTS variant mutation; or~~
- ~~a first, second, or third-degree relative diagnosed with LQTS by clinical means but in whom the genetic status is unavailable; or~~
- ~~signs and/or symptoms indicating a moderate-to-high pretest probability (i.e. Schwartz score of 2-3) of LQTS.~~

~~Short QT Syndrome~~

~~Genetic testing in patients with suspected congenital long QT syndrome (LQTS) may be considered medically necessary for the following indications:~~

- ~~members with signs and/or symptoms of SQTS, but a definitive diagnosis cannot be made without genetic testing; or~~
- ~~members who do not meet the clinical criteria for SQTS but who have a first, second, or third-degree relative with a known LQTS variant mutation~~

~~Catecholaminergic Polymorphic Ventricular Tachycardia~~

~~Genetic testing for catecholaminergic polymorphic ventricular tachycardia (CPVT) may be considered medically necessary for members who do not meet the clinical criteria for CPVT but who have:~~

- ~~a first, second, or third-degree relative with a known CPVT variant mutation; or~~
- ~~a first, second, or third-degree relative diagnosed with CPVT by clinical means but in whom the genetic status is unavailable; or~~
- ~~member with exercise, catecholamine, or emotion induced PVT or ventricular fibrillation, with a structurally normal heart~~
- ~~signs and/or symptoms indicate a moderate-to-high pretest probability of CPVT~~

~~Brugada Syndrome~~

~~Genetic testing for Brugada syndrome (BrS) is considered medically necessary when documentation in the medical record indicates that all of the following criteria are met:~~

- ~~The member has a type 1 Brugada ECG pattern that appears spontaneously or after the administration of an antiarrhythmic drug; or~~
- ~~The member has one of the following:~~
  - ~~A first or second- degree relative with a known BrS variant mutation; or~~
  - ~~A first or second-degree relative with sudden death due to BrS; or~~
  - ~~For the purposes of identifying a BrS mutation that can be used for family-specific screening in at-risk blood relatives.~~

Cardiomyopathies:

The member has a personal history of ANY of the following clinical features or diagnoses:

1. Hypertrophic Cardiomyopathy (HCM)
2. Dilated Cardiomyopathy (DCM)
3. Restrictive Cardiomyopathy (RCM)
4. Arrhythmogenic cardiomyopathy (ACM) not secondary to ischemic, hypertensive, or valvular heart disease, such

arrhythmogenic right/left ventricular cardiomyopathy (ARVC/ALVC), cardiac amyloidosis, sarcoidosis, and left ventricular noncompaction (LVNC).

5. Member has sub-clinical signs suggestive of HCM, DCM, RCM, or ACM AND a first degree or second-degree relative with a cardiomyopathy.

The member has a family history of ANY of the following diagnoses:

1. One first- or second- degree relative with a known history of sudden cardiac arrest or death <40y; or
2. Two or more relatives on the same side of the family with history sudden cardiac arrest or death at any age; OR
3. A first, second, or third degree relative with a known mutation in a cardiomyopathy gene for which medical management may impact the member's cardiac surveillance strategy.
4. Two or more first, second, or third degree relatives with a reported cardiomyopathy but genetic testing may have not been completed or the report is unavailable to direct testing.

~~Left Ventricular Noncompaction~~

~~Genetic testing for left ventricular noncompaction (LVNC) is considered medically necessary when:~~

- ~~signs and/or symptoms consistent with LVNC are present, but a definitive diagnosis cannot be made without genetic testing; or~~
- ~~a first, second, or third-degree relative has a known LVNC variant mutation.~~

~~Hypertrophic Cardiomyopathy~~

~~Genetic testing for hypertrophic cardiomyopathy (HCM) is considered medically necessary when:~~

- ~~members are at risk for development of HCM due to a first-degree relative with established HCM and a known pathogenic gene variant mutation is present.~~

~~Dilated Cardiomyopathy~~

~~Genetic testing for dilated cardiomyopathy is considered medically necessary for members who:~~

- ~~have dilated cardiomyopathy and significant cardiac conduction disease (i.e. first-, second, or third-degree heart block); or~~
- ~~have one or more family members who experienced sudden cardiac death or developed unexplained heart failure before age 60.~~

~~Genetic testing for a known familial mutation associated with dilated cardiomyopathy is considered medically necessary in asymptomatic first, second, or third-degree relatives of a proband.~~

~~Restrictive Cardiomyopathy~~

~~Genetic testing for a known familial mutation associated with restrictive cardiomyopathy (RCM) is considered medically necessary in asymptomatic first, second, or third-degree relative of a proband.~~

~~Right Ventricular Cardiomyopathy~~

~~Genetic testing for arrhythmogenic right ventricular cardiomyopathy (ARVC) is considered medically necessary:~~

- ~~When signs and/or symptoms consistent with ARVC are present, but a definitive diagnosis cannot be made without genetic testing; or~~
- ~~Member has a first, second, or third-degree relative with a known ARVC variant mutation.~~

MP316 High Intensity Focused Ultrasound and Laser – (Revised) – Add Indication

High-intensity focused ultrasound (HIFU) may be considered medically necessary as a local treatment for prostate cancer when all of the following criteria are met:

- radiation therapy recurrence; and
- the member is a candidate for local therapy (e.g., life expectancy > 5y); and
- transrectal ultrasound guided (TRUS) biopsy positive; and
- there is an absence of metastatic disease

MP324 Genetic Testing for Disease Carrier Status – (Revised) – Extensive Revisions

DESCRIPTION: Genetic testing for the purposes of carrier status screening is performed to identify genetic risk that may impact reproductive decision-making. Individuals identified as being "carriers" are typically not affected by the condition but have an increased risk of having a child with a genetic condition. Genetic testing for carrier status ~~screening~~ may be available for autosomal recessive genetic conditions, X chromosome-linked conditions, and certain other chromosomal abnormalities.

The cost of carrier screening for an individual condition may be higher than the cost of testing for multiple conditions through expanded carrier screening panels. When selecting a carrier screening approach, the cost of each option to the patient and the health care system should be considered.

Universal carrier screening, regardless of ethnic background, is considered medically necessary for members and their current reproductive partner. Many genetic syndromes are a public health issue in today's pan-ethnic population, and ethnicity-based testing is no longer the recommended approach.

GENERAL INDICATIONS:
Genetic testing for inheritable diseases, offered in a setting with appropriately trained health care professionals who can provide pre- and post-test counseling, and performed by a qualified laboratory, is considered to be medically necessary when:

- Based on family history, pedigree analysis, risk factors, and / or signs or symptoms, there is a reasonable expectation that a genetically inherited condition exists; and
- The testing methodology is considered a proven method for the identification of a genetically-linked disease; and
- The test results will guide disease treatment decisions or prevention strategies**.**
- The test result(s) will guide reproductive risks, fetal outcomes, treatment for the fetus, parent, or parent(s) of the pregnant couple, or birth plan

SPECIFIC INDICATIONS:

Carrier Screening During or Before Pregnancy:

Genetic Screening:

Universal carrier screening via genetic sequencing is considered medically necessary in the following scenarios:

1. The member is currently pregnant, OR
2. The member's current reproductive partner is pregnant (see below), OR
3. Preconception planning for a member AND their current reproductive partner, OR
4. Family member with known recessive genetic syndrome or known carrier of recessive disease; OR
5. Ethnicity-based screening has been completed previously but was limited to specific or targeted variants and the results were uninformative.

AND

The genetic test includes at least:

I. cystic fibrosis (CF) AND spinal muscular atrophy (SMA); OR
II. The single gene concern based on family history of a specific syndrome for which an association with a disorder has medical management impacts (example: Tay-Sach's disease, rare recessive disorders),

Hemoglobinopathies (alpha thalassemia, beta thalassemia, sickle cell disease or trait)

Universal screening for hemoglobinopathies via complete blood count is considered medically necessary if the member is pregnant, has a reproductive partner who is pregnant, or the member is planning pregnancy.

1. A Complete Blood Count (CBC) with red blood cell indices should be performed in all people who are members who are currently pregnant OR considering future pregnancy.
2. Hemoglobin electrophoresis is medically necessary when CBC results demonstrate a low mean corpuscular volume (MCV) CBC and/or are suggestive of any hemoglobinopathy.
3. Genetic sequencing is not recommended as a first-line approach after abnormal CBC but may be considered when universal genetic carrier screening is performed as a cost-saving approach.

Fragile X syndrome:

1. Diagnostic testing of the FMR1 gene related to for Fragile X syndrome is considered medically necessary for the member, in the following scenarios:
    a. personal or family history of unexplained ovarian insufficiency or elevated FSH <40y; OR
    b. family history of intellectual disability; OR
    c. known family history of Fragile X syndrome or carrier status in any 1st, 2nd, or 3rd degree relative; OR
    d. the member has no clinical signs or symptoms related to Fragile X syndrome in their personal or family history, but universal carrier screening is already being performed.
2. Carrier screening for specific syndromes, called ("single gene testing" or "targeted testing)" can be considered medically necessary if there is a reported family history in the member's 1st, 2nd, or 3rd degree biological relative.
3. Ashkenazi Jewish Carrier Screening Panel may be offered in individuals who report any percentage Ashkenazi Jewish heritage.

a. (Examples include: Canavan Disease, Fabry Disease, Gaucher Disease, Bloom syndrome, Maple Syrup Urine disease, Cystic Fibrosis, Glycogen Storage disease type 1, Familial Dysautonomia, Franconi Anemia, Mucolipidosis IV, Friederich Ataxia, Niemann-Pick Disease, Tay-Sachs Disease, Tuberous Sclerosis)
b. At least one partner of a couple is of Ashkenazi Jewish heritage
c. (NOTE: If only one partner of a couple is Ashkenazi Jewish, testing should start in that person when possible.)

Reproductive Partner of the Pregnant Person:

1. Universal carrier screening for spinal muscular atrophy (SMA) and/or cystic fibrosis (CF) in a pregnant person's reproductive partner is considered medically necessary in today's pan-ethnic population.
2. Targeted carrier screening through single gene testing, or testing for specific syndromes, is considered medically necessary when:
   a. The member has a known mutation (P/LP variant) in a gene associated with a recessive genetic syndrome.
      i. Common Examples: Tay-Sachs disease, Cystic Fibrosis, Spinal Muscular Atrophy, Noonan syndrome, other genetic syndromes with known recessive inheritance..

OR

   b. The member has a known mutation in a gene associated with risk for a dominant hereditary cancer syndrome where biallelic variants cause risk for a recessive, pediatric-onset, hereditary cancer syndrome.

Condition	Gene	Risk to Pregnancy
Ataxia Telangiectasia	ATM	AT is characterized by progressive cerebellar ataxia with onset in early childhood, telangiectasias, immune defects, and a predisposition to malignancy.
Fanconi Anemia	BRCA1, BRCA2, PALB2, BRIP1, RAD51C	Fanconi anemia is characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. Bone marrow failure with pancytopenia often presents in the first decade of life.
Constitutional Mismatch Repair Deficiency	MLH1, MSH2, MSH6, PMS2, EPCAM	CMMRD is a childhood cancer predisposition syndrome characterized by hematologic malignancies, brain/central nervous system tumors, colorectal tumors and multiple intestinal polyps, and other malignancies including embryonic tumors and rhabdomyosarcoma.
Fumarate Hydratase deficiency	FH	Inborn error of metabolism characterized by rapid neurologic impairment, hypotonia, seizures, and cerebral atrophy.
Mitochondrial Complex II Deficiency Syndrome	SDHA, SDHB, SDHD	Characterized by neurodegeneration and encephalomyopathy.

~~Tay-Sachs disease:~~

~~Genetic testing of the HEXA gene may be considered medically necessary when one or more of the following criteria are met:~~

- Symptomatic member with clinical features suggestive of TSD or variants and abnormal HEX A or HEX B enzymatic testing, but after conventional studies a definitive diagnosis remains uncertain.
- To detect a pseudodeficiency allele in an asymptomatic member with abnormal HEX A or HEX B enzymatic testing
- Member with a first or second-degree relative with a confirmed TSD or variant
- Members with reproductive partners with chronic or adult-onset HEXA or HEXB deficiency with the intention to reproduce
- Members who are pregnant or whose reproductive partner is pregnant or planning a pregnancy when one or more of the following criteria apply:
    - At least one of the couple is of Ashkenazi Jewish origin
    - At least one of the couple is of Cajun or Acadian origin
    - At least one of the couple is of French-Canadian origin
    - At least one of the couple is affected with or is a known carrier of Tay-Sachs disease
    - There is a positive family history of Tay-Sachs disease

Cystic Fibrosis

Genetic testing of the CFTR gene may be considered medically necessary when one or more of the following criteria are met:

- Member with a negative sweat test who exhibit symptoms of CF
- Male members with congenital bilateral absence of the vas deferens
- Infant members with symptoms consistent with CF who are too young to accomplish a sweat chloride test
- Members who are pregnant or whose reproductive partner is pregnant or are planning a pregnancy

Hemoglobinopathies (Sickle Cell Anemia, Alpha/beta thalassemia)

Genetic testing may be considered medically necessary when one or more of the following criteria are met:

- Family history of hemoglobinopathy with known mutation
- Hemoglobinopathy is suspected after complete blood count and hemoglobin analysis and the member has origins in a high-risk group (eg, African American, African, Asian, Middle eastern, Carribbean, or Mediterranean descent)

Ashkenazi Jewish Carrier Screening Panel

(Canavan Disease, Fabry Disease, Gaucher Disease, Bloom syndrome, Maple Syrup Urine disease, Cystic Fibrosis, Glycogen Storage disease type 1, Familial Dysautonomia, Franconi Anemia, Mucolipidosis IV, Friederich Ataxia, Niemann-Pick Disease, Tay-Sachs Disease, Tuberous Sclerosis)

Panel testing may be considered medically necessary when the following criteria are met:

- The member is planning a pregnancy or currently pregnant; and
- At least one partner of a couple is of Ashkenazi Jewish heritage (NOTE: If only one partner of a couple is Ashkenazi Jewish, testing should start in that person when possible.)

Single Ashkenazi Jewish Genetic Diseases Carrier Screening Tests

Single gene carrier screening may be considered medically necessary when:

- The member has a family history of one of the conditions listed in the panel; OR
- The member's partner is a known carrier or affected with any of the conditions listed in the panel

Duchenne muscular dystrophy/Becker muscular dystrophy

Genetic testing may be considered medically necessary when one or more of the following criteria are met:

- In a male member with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment.

- For at-risk female member relatives defined as first- and second-degree female relatives and include the proband's mother, female siblings of the proband, female offspring of the proband, the proband's maternal grandmother, maternal aunts and their offspring.

Fragile X syndrome

Genetic testing may be considered medically necessary when one or more of the following criteria are met:

- Members of either sex with intellectual disability, developmental delay or autism spectrum disorder
- Members seeking reproductive counseling who have a family history of fragile X syndrome or a family history of undiagnosed intellectual disability
- Prenatal testing of fetuses in pregnant members who are known carriers
- Affected members who have had a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status
- Members with unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before the age of 40

Neurofibromatosis type 1 and 2

Genetic testing for neurofibromatosis type 1 may be considered medically necessary when the diagnosis is clinically suspected due to signs of disease, but a definitive diagnosis cannot be made without genetic testing.

The member must meet one of the following:

- A first-, second- or third-degree relative has a known NF mutation; or
- A first-, second- or third-degree relative has been diagnosed with neurofibromatosis but whose genetic status is unavailable

Or

The member meets at least two of the following criteria:

- six or more light brown spots on the skin ("cafe-au-lait" spots), measuring more than 5 mm in diameter in children or more than 15 mm across in adolescents and adults;
- two or more neurofibromas, or one plexiform neurofibroma (a neurofibroma that involves many nerves);
- freckling in the area of the armpit or the groin;
- two or more growths on the iris of the eye (Lisch nodules or iris hamartomas);
- a tumor on the optic nerve (optic nerve glioma);
- abnormal development of the spine (scoliosis), the temple (sphenoid) bone of the skull or the tibia;
- a parent, sibling or child with NF1

Genetic testing for neurofibromatosis type 2 is medically necessary when the diagnosis is clinically suspected due to signs of disease, but a definitive diagnosis cannot be made without genetic testing. The member must meet one of the following criteria:

- Members with a first degree relative with NF2 (i.e., affected parent, sibling or offspring)
- Multiple spinal tumors (schwannomas, meningiomas)
- Cutaneous schwannomas
- Sporadic vestibular schwannoma less than 30 years of age, or spinal tumor or meningioma less than 20 years of age
- Unilateral vestibular schwannoma in those less than 20 years of age

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL);

Genetic testing to confirm the diagnosis of CADASIL syndrome may be considered medically necessary when:

- Clinical signs, symptoms and imaging results indicate the pre-test probability of CADASIL is moderate to high (total score of 14)*; or
- The diagnosis of CADASIL is inconclusive following alternate methods of testing, including MRI and skin biopsy

Features	***Points***
Migraine	*1*
Migraine with aura	*3*
Psychiatric disturbance	*1*
Transient ischemic attack/stroke	*1 (2 if <50yo)*
Subcortical infarcts	*2*
Cognitive decline	*3*
LE (leukoencephalopathy)	*3*
LE extended to temporal pole	*1*
LE extended to external capsule	*5*

Pooled Frequency of Clinical and Radiologic Features (Pescini et al., 2012)

Charcot-Marie-Tooth:

Genetic Testing for Charcot-Marie-Tooth (CMT) disease is medically necessary when the member has clinical features of CMT and a definitive diagnosis remains uncertain after history, physical examination, genetic counseling and completion of nerve conduction studies and/or electromyography.

- If nerve conduction studies of ulnar/median nerve indicate demyelinating neuropathy (velocity <38 m/s), test for the most commonly identified CMT subtype: CMT1A (PMP22 duplication).
- If the result is negative, multi-gene panel testing of genes GJB1 (CMTX1), MPZ (CMT1B), MFN2 (CMT2A2), LITAF (CMT1C), EGR2 (CMT1D), PMP22 sequencing (CMT1E), GARS (CMT2D), NEFL (CMT2E/1F), GDAP1 (CMT2H/2K) and SH3TC2 (CMT4C).
- If nerve conduction studies of ulnar/median nerve indicate axonal neuropathy (velocity >38 m/s), multi-gene panel testing of genes GJB1 (CMTX1), MPZ (CMT1B), LITAF (CMT1C), EGR2 (CMT1D), PMP22 sequencing (CMT1E), MFN2 (CMT2A2), GARS CMT2D), NEFL (CMT2E/1F), GDAP1 (CMT2H/2K) and SH3TC2 (CMT4C)

Alpha-1-antitrypsin deficiency:

Genetic testing for alpha-1 antitrypsin deficiency may be considered medically necessary when the member meets either criteria 1 or 2, and 3:

1. alpha-1 antitrypsin deficiency is suspected in member presenting with clinical factors such as:
   - Early-onset emphysema (45 years or younger); or
   - Emphysema without history of risk factors (smoking, occupational exposure, etc.); or
   - Emphysema with prominent basilar hyperlucency; or
   - Bronchiectasis of unknown etiology; or
   - liver disease of unknown etiology; or
   - Anti-proteinase 3-positive vasculitis; or
   - Necrotizing panniculitis

Or;

2. Member is at risk due to a first-degree relative with alpha-1 antitrypsin deficiency

AND

3. Member has a serum alpha-1 antitrypsin level in the range of severe deficiency

Phenotype	**AAT Blood Level**
MM	20–53 µM | 150–350 Mg/dL
MZ	12–28 µM | 90–210 Mg/dL
SS	13–27 µM | 100–210 Mg/dL

SZ 10–16 µM | 75–120 Mg/dL
ZZ 2.5–7 µM | 20–45 Mg/dL
NULLNULL 0 µM | 0 Mg/dL

Neimann – Pick Disease:

Genetic testing for SMPD1 and NPC1 gene may be considered medically necessary in either of the following populations:

- Symptomatic members with clinical features suggestive of NPD and abnormal biochemical testing, but a definitive diagnosis remains uncertain after completion of conventional studies.
- First- or second-degree relative members with the capacity and desire to reproduce once the mutations have been identified in the proband.

Primary Dystonia Type 1:

Genetic testing for DYT1 gene sequence variants may be considered medically necessary in either of the following populations:

- Members with documented onset of primary dystonia at or before age 30 years
- Members with documented onset of primary dystonia at age 30 years or later with a relative who developed dystonia at 30 years or younger

Prader-Willi Syndrome

Genetic testing may be considered medically necessary in symptomatic pediatric members for diagnosis of Prader-Willi syndrome or in symptomatic adult members when all of the following criteria are met:

- Documented history of hypotonia and poor suck
- Global developmental delay

Angelman Syndrome

Genetic testing to confirm the absence of maternally expressed gene(s) located on chromosome 15 within bands q11.2 to q13 may be considered medically necessary in symptomatic pediatric members for diagnosis of Angelman Syndrome or in symptomatic adult members when all of the following criteria are met:

- Documentation of absence of major birth defects with normal head circumference
- Evidence of developmental delay by age 6 to 12 months
- Delayed progression and attainment of developmental milestones without overall loss of skills
- Normal metabolic, hematologic and chemical laboratory studies
- Normal brain structure as evidenced by CT or MRI
- Absent or severely impaired speech
- Balance disorder with ataxia or tremulous movement of limbs
- Documentation of behavioral characteristics such as inappropriate happy demeanor, frequent and inappropriate laughter or smiling, short attention span, excitability, hand-flapping, or hypermotor activity

Gaucher disease

Genetic testing may be considered medically necessary as follows:

Diagnostic Testing for Symptomatic members:

- Glucosylceramidase enzyme activity in peripheral blood leukocytes is 0 - 15% of normal activity, and
  - bone changes including osteopenia, focal lytic or sclerotic bone lesions or osteonecrosis; or
  - Liver/spleen enlargement and anemia or thrombocytopenia; or
  - Primary neurologic disease including one or more of the following:
    - cognitive impairment,
    - pyramidal signs (e.g., spasticity, hyperactive reflexes)

- bulbar signs (e.g., dysphagia, dysarthria, dysphonia, etc)
- eye movement disorders,
- seizures

Diagnostic Testing for members who are Asymptomatic Carriers:
- a mutation is detected by targeted mutation analysis, and
- Glucosylceramidase enzyme activity in peripheral blood leukocytes is 0-15% of normal activity,

Testing for Members with Family History or Partners of Carriers:
- 1st, 2nd, or 3rd degree biologic relative with confirmed Gaucher diagnosis, or
- the member has the intention to reproduce with a partner who is monoallelic or biallelic for GBA mutation

Huntington's disease

Genetic testing related to Huntington's disease may be considered medically necessary for:

a) Confirmatory testing in members with clear symptoms and positive family history; or
b) Diagnostic testing in members with no family history of the disease, but who exhibit symptoms consistent with Huntington's disease such as:
   - Involuntary jerking movements
   - Impaired gait, posture and balance
   - Dystonia
   - Cognitive disorders

Rett syndrome:

Genetic testing may be considered medically necessary when:
- The member meets the clinical diagnostic criteria for Rett syndrome; and
- Gene testing is necessary to confirm diagnosis due to clinical uncertainty

Peutz-Jeghers Syndrome:

Genetic testing may be considered medically necessary when:

There is a known family history of STK11 (LKB1) gene mutation; or
The member has a clinical diagnosis of PJS based on **at least TWO of the following** features:
- At least TWO PJS-type hamartomatous polyps of the gastrointestinal tract; or
- Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers; or
- A family history of PJS.

Noonan Syndrome:

Genetic testing via panel may be considered medically necessary when:
There is a known family history of TPN11, SOS1, RADF1 and KRAS gene mutation; or
The member is suspected of Noonan syndrome due to a combination of **any** of the following:
- A characteristic facial appearance.
- Short stature.
- Heart defect present at birth (congenital heart defect).
- A broad or webbed neck.
- Minor eye problems such as strabismus in up to 95 percent of individuals.
- Bleeding problems such as a history of abnormal bleeding or bruising.
- An unusual chest shape with widely-spaced and low set nipples.
- Developmental delay of varying degrees, but usually mild.
- Undescended testes
- There is a known family history of TPN11, SOS1, RADF1 and KRAS gene mutation

Spinal Muscular Atrophy:

~~Genetic testing may be considered medically necessary for the indications of:~~

~~Diagnostic testing in members with:~~
- ~~hypotonia and weakness (symmetrical but proximal greater than distal); and~~
- ~~abnormal deep tendon reflexes (severely decreased or absent)~~

~~Carrier testing:~~
- ~~Members with a family history of SMA or disease suspicious for SMA; or~~
- ~~Member with a blood relative who is a known carrier or diagnosed with SMA and has a known SMA mutation; or~~
- ~~Member who is pregnant or is planning a pregnancy~~
- ~~Members whose reproductive partner has a known carrier status~~

~~Prenatal testing in members who are pregnant and both partners are known carriers~~

~~Marfan Syndrome Loeys-Dietz Syndrome, Ehlers-Danlos Syndrome~~
~~Genetic testing may be considered medically necessary when:~~
- ~~There is a known family pathogenic variant; **or**~~
- ~~The member presents with signs and symptoms consistent with Marfan syndrome Loeys-Dietz Syndrome, or Ehlers-Danlos Syndrome but a definitive diagnosis cannot be established.~~

~~And~~
- ~~Targeted mutation testing limited to 1 or more of the following is planned: FBN1, MYH11, ACTA2, COL3A1,~~
~~SLC2A10, SMAD3, MYLK, TGFBR1, and TGFBR2~~

EXCLUSIONS:
Direct-to-consumer genetic testing, or “home testing” kits, are NOT COVERED.

Genetic testing for the diagnosis or risk assessment of Alzheimer's disease is considered experimental, investigational or unproven and therefore NOT COVERED. There is insufficient published peer reviewed medical literature to support the efficacy of genetic testing in Alzheimer’s disease.

Whole Genome Sequencing (WGS) - Please reference MP280: Whole Exome Sequencing ~~REQUIRES PRIOR AUTHORIZATION BY A PLAN MEDICAL DIRECTOR OR DESIGNEE~~

~~Whole Genome Sequencing (WGS) is an evolving technology, but currently has limited application outside of a research setting and is generally considered to be unproven for the purposes of screening and evaluating genetic disorders. There is currently insufficient evidence to support the efficacy is using WGS for routine evaluations. Consideration of requests for WGS will be done on a “per-case” basis.~~

MP325 Genetic Testing for Familial Hypercholesterolemia – (Revised) – Extensive Revisions

DESCRIPTION: Familial hypercholesterolemia is an inherited genetic condition that results in a >20-fold increase in risk for premature or “early-onset” atherosclerotic cardiovascular disease events (ASCVD) due to lifelong exposure to elevated low-density lipoprotein cholesterol (LDL-C). The condition encompasses a spectrum of clinical phenotypes with a broad range of pathogenic variants.

Disease-specific panels may change form year to year based on available evidence and technological advancements. Germline multigene panel testing (MGPT) for moderate and high-penetrance familial hypercholesterolemia susceptibility genes should include LDLR, APOB, and PCSK9. Test methodology should include sequencing and full deletion and duplication analysis (i.e., detection of large genomic rearrangements) with a benefit of once per lifetime, dependent upon advances in testing technology.

~~**Targeted Populations:**~~

~~Children (defined as less than age 18 years) with:~~

- ~~persistent LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia); or~~
- ~~with an LDL-C level ≥190 mg/dl in ≥1 parent; or~~
- ~~a family history of hypercholesterolemia and premature CAD.~~

~~Adults (defined as 18 years or older) with:~~

- ~~persistent LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia); and~~
- ~~a family history of hypercholesterolemia; and~~
- ~~a personal history **or** a family history of premature CAD~~

~~Adults (defined as 18 years or older) with:~~

- ~~no pretreatment LDL-C levels available; and,~~
- ~~a personal history of premature CAD; and~~
- ~~family history of both hypercholesterolemia and premature CAD~~.

INDICATIONS: Genetic Testing for Familial Hypercholesterolemia or inherited dyslipidemias will be considered medically necessary in a member when any of the following criteria are met:

1. The member meets diagnostic criteria per MedPed, Simon Broome, or Dutch Lipid Clinic tools (below)

OR

2. Elevated LDL-C level, defined as:
   1. An LDL-C level of >160mg/dL in a member <18y, without an apparent secondary cause, **OR**
   2. A pre-treatment LDL-C level of >190mg/dL without an apparent secondary cause, in a member >18y, **OR**A post-treatment LDL-C level of >130mg/dl with no pre-treatment LDL-C available at any age, OR
   3. Failure to achieve LDL-C goal with at least one line of acceptable therapy
   4. An LDL-C level of >130mg/dL at any age, with ≥1 close relative(s) with known or suspected FH.

OR

3. Elevated total cholesterol, defined as:
   1. A total cholesterol level of >230mg/dL in a member <18y, without an apparent secondary cause, **OR**
   2. A pre-treatment total cholesterol level of >310mg/dL, in a member >18y, without an apparent secondary cause.

OR

4. A personal history of premature coronary artery disease (CAD) such as myocardial infarction or obstructive CAD requiring intervention or other cardiovascular disease (e.g., ischemic stroke, peripheral vascular disease) in:
   1. A <55y assigned-male at birth member, OR
   2. A <65y in assigned-female at birth member, OR
   3. A member without personal history of CAD, but reports with 2 or more close relatives on the same side of the family meeting the above criteria.

OR

5. A personal history of 1 or more physical features:
   1. corneal arcus reported before age 45y

2. xanthoma(s) or xanthelasma(s)

OR

6. A family history of molecularly confirmed FH with a variant in APOB, LDLR, PCSK9 in a first, second, or third degree relative and directed (targeted variant) testing is unable to be performed.

~~LDLR, APOB, PCSK9 Known Familial Mutation Testing~~ ~~will be considered medically necessary when all of the following criteria are met:~~

- ~~Clinical consultation and genetic counseling by an appropriate provider has been completed; and~~
- ~~Member has not had previous genetic testing of LDLR, APOB, or PCSK9; and~~
- ~~LDLR, APOB, or PCSK9 mutation has been identified in a 1st, 2nd or 3rd degree biological relative; and~~
- ~~Member has LDL cholesterol of >120 mg/dL in the absence of treatment~~
- ~~The result of the test will directly impact the treatment being delivered to the member.~~

~~LDLR Full Sequence and Deletion/Duplication Analysis~~ ~~will be considered medically necessary when all of the following criteria are met:~~

- ~~Clinical consultation and genetic counseling by an appropriate provider has been completed; and~~
- ~~Member has not had previous LDLR sequencing or deletion/duplication testing; and~~
- ~~There is no known LDLR, APOB, or PCSK9 mutation in the family, and~~
- ~~The member meets the MEDPED criteria or either the Dutch criteria or the Simon Broome criteria for possible or probable FH; and~~
- ~~Genetic testing is necessary because there is uncertainty in the clinical diagnosis~~

~~APOB Targeted Mutation Analysis or Full Sequence Analysis~~ ~~will be considered medically necessary when all of the following criteria are met:~~

- ~~Criteria for LDLR sequencing and deletion/duplication analysis is met; and~~
- ~~No previous full sequence analysis of APOB; and~~
- ~~No mutations detected in full sequencing or deletion/duplication testing of LDLR or PCSK9 sequencing, if previously performed~~

~~PCSK9 Full Sequence Analysis~~ ~~will be considered medically necessary when all of the following criteria are met:~~

- ~~Criteria for LDLR sequencing and deletion/duplication analysis is met; and~~
- ~~No previous genetic testing for PCSK9; and~~
- ~~No mutations detected in full sequencing or deletion/duplication analysis of LDLR or APOB sequencing, if previously performed~~

LDLR, APOB, PCSK9 multi-gene panels, or FH multi-gene panels, are the preferred approach for evaluation of FH, unless there is a known familial variant.

A familial hypercholesterolemia panel is ~~will be~~ considered medically necessary when all of the following criteria are met:

- The member meets ANY of the above listed criteria for evaluation of familial hypercholesterolemia (FH); and
- Clinical consultation and genetic counseling by an appropriate provider has been completed; and
- Member has not had previous LDLR, APOB, or PCSK9 sequencing or deletion/duplication testing, and
- There is no known LDLR, APOB, or PCSK9 mutation in the family, ~~and~~

- ~~The member meets the MEDPED criteria or either the Dutch criteria or the Simon Broome criteria for possible or probable FH, and~~
- ~~Genetic testing is necessary because there is uncertainty in the clinical diagnosis~~

LDLR, APOB, PCSK9, LDLRAP1 Known Familial Mutation Testing is considered medically necessary when all of the following criteria are met:

- LDLR, APOB, or PCSK9 mutation has been identified in a 1st, 2nd or 3rd degree biological relative; and
- Genetic counseling by an appropriate provider has been completed in the member, or if the member is <18, genetic counseling has been provided to the parent or legal guardian(s); and
- The member has not had previous genetic testing of LDLR, APOB, or PCSK9; and
- The result of the test will directly impact the treatment timeline and/or options for the member.

MP327 Autonomic Testing – (Revised) – Add Exclusion

EXCLUSIONS:
Autonomic testing using automated devices, in which software automatically generates an interpretation, has not been validated (e.g., ANSAR ANX 3.0, SUDOSCAN, VitalScan, Neuropad, EZScan, or electrochemical skin conductance [ESC]). There is insufficient evidence in the published, peer-reviewed medical literature to support the use of these devices. They are therefore considered to be experimental, investigational or unproven and **NOT COVERED**.

There is insufficient evidence in the published, peer-reviewed medical literature to support the use of Quantitative pilomotor axon reflex test (QPART) for evaluating pilomotor function. There is insufficient evidence in the published, peer-reviewed medical literature to support the clinical value of this testing. It is therefore considered to be experimental, investigational or unproven and **NOT COVERED**.

MP374 Genetic Testing for Inheritable Diseases – (NEW)

Genetic Syndromes

Description:

General Indications: Genetic testing for inheritable diseases, offered in a setting with appropriately trained health care professionals who can provide pre- and post-test counseling, and performed by a qualified laboratory, is considered to be medically necessary when:

- Based on family history, pedigree analysis, risk factors, and / or signs or symptoms, there is a reasonable expectation that a genetically inherited condition exists; and
- The testing methodology is considered a proven method for the identification of a genetically-linked disease; and
- The test results will guide disease treatment decisions or prevention strategies.

Connective Tissue Disorders

Marfan Syndrome Loeys-Dietz Syndrome, Ehlers-Danlos Syndrome

Genetic testing may be considered medically necessary when:

- There is a known family pathogenic variant; **or**
- The member presents with signs and symptoms consistent with Marfan syndrome Loeys-Dietz Syndrome, or Ehlers-Danlos Syndrome but a definitive diagnosis cannot be established.

And

- Targeted mutation testing limited to 1 or more of the following is planned: *FBN1, MYH11, ACTA2, COL3A1, SLC2A10, SMAD3, MYLK, TGFBR1, and TGFBR2*

Pediatric-Onset genetic syndromes

Tay-Sachs disease:

Genetic testing of the HEXA gene may be considered medically necessary when there is a high degree of clinical suspicion for Tay-Sachs disease, otherwise, panel testing is otherwise a more effective approach for evaluation of progressive weakness or motor decline.

If Tay-Sachs is suspected based on clinical features:

1. Enzyme testing of HEX A and HEX B is recommended as a first line test.
2. In pregnant women or women taking oral contraceptives, enzyme testing should be performed on leukocytes; serum testing has increased chances of false positives.
3. If there is no or extremely low HEX A, proceed to HEXA gene sequencing
4. If there is residual enzyme activity, recommend panel testing that includes HEXA and other genes involved in progressive neuromuscular decline.

One or more of the following criteria must be met:

- Symptomatic member with clinical features suggestive of TSD AND abnormal HEX A or HEX B enzymatic testing, but after conventional studies a definitive diagnosis remains uncertain.
- To detect a pseudodeficiency allele in an asymptomatic member with abnormal HEX A or HEX B enzymatic testing
- Member with a first or second-degree relative with a confirmed TSD or variant

Cystic Fibrosis

Genetic testing of the *CFTR* gene may be considered medically necessary when one or more of the following criteria are met:

- Member with a negative sweat test who exhibit symptoms of CF
- Member with clinical features suggestive of CF with prior negative or uninformative genotyping
- Male members with congenital bilateral absence of the vas deferens
- Infant members with a positive newborn screening test, or symptoms consistent with CF and are too young to accomplish a sweat chloride test

Spinal Muscular Atrophy:

Diagnostic genetic testing of SMN1 and/or SMN2 may be considered medically necessary in members with:

- hypotonia and weakness (symmetrical but proximal greater than distal); and
- abnormal deep tendon reflexes (severely decreased or absent)

  OR
- an asymptomatic neonate when the member's parents when one or both are known carriers

Hemoglobinopathies (Sickle Cell Anemia, Alpha- Beta thalassemia)

Genetic testing may be considered medically necessary when one or more of the following criteria are met:

- Hemoglobinopathy is suspected based on abnormal complete blood count AND hemoglobin electrophoresis is complete.
- Family history of sickle cell disease or trait, alpha thalassemia, beta thalassemia, or other hemoglobinopathy with known mutation

Duchenne muscular dystrophy/Becker muscular dystrophy

Genetic testing may be considered medically necessary when one or more of the following criteria are met:

- In a male member with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment.
- For at-risk female member relatives defined as first- and second-degree female relatives and include the proband's mother, female siblings of the proband, female offspring of the proband, the proband's maternal grandmother, maternal aunts and their offspring.

Neimann – Pick Disease:

Genetic testing for SMPD1 and NPC1 gene may be considered medically necessary in either of the following populations:

- Symptomatic members with clinical features suggestive of NPD and abnormal biochemical testing, but a definitive diagnosis remains uncertain after completion of conventional studies.
- First- or second-degree relative members with the capacity and desire to reproduce once the mutations have been identified in the proband.

Primary Dystonia Type 1:

Genetic testing for DYT1 gene sequence variants may be considered medically necessary in either of the following populations:

- Members with documented onset of primary dystonia at or before age 30 years
- Members with documented onset of primary dystonia at age 30 years or later with a relative who developed dystonia at 30 years or younger

Gaucher disease

Genetic testing may be considered medically necessary as follows:

Diagnostic Testing for Symptomatic members:

- Glucosylceramidase enzyme activity in peripheral blood leukocytes is 0 - 15% of normal activity, and
    - bone changes including osteopenia, focal lytic or sclerotic bone lesions or osteonecrosis; or
    - Liver/spleen enlargement and anemia or thrombocytopenia; or
    - Primary neurologic disease including one or more of the following:
        - cognitive impairment,
        - pyramidal signs (e.g., spasticity, hyperactive reflexes)
        - bulbar signs (e.g., dysphagia, dysarthria, dysphonia, etc)
        - eye movement disorders,
        - seizures

Diagnostic Testing for members who are Asymptomatic Carriers:

- a mutation is detected by targeted mutation analysis, and
- Glucosylceramidase enzyme activity in peripheral blood leukocytes is 0-15% of normal activity,

Fragile X syndrome

Genetic testing may be considered medically necessary when one or more of the following criteria are met:

- Members of either sex with intellectual disability, developmental delay or autism spectrum disorder
- Members seeking reproductive counseling who have a family history of fragile X syndrome or a family history of undiagnosed intellectual disability
- Prenatal testing of fetuses in pregnant members who are known carriers
- Affected members who have had a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status
- Members with unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before the age of 40

Neurofibromatosis type 1 and 2

Genetic testing for neurofibromatosis type 1 may be considered medically necessary when the diagnosis is clinically suspected due to signs of disease, but a definitive diagnosis cannot be made without genetic testing.

The member must meet one of the following:

- A first-, second- or third-degree relative has a known NF mutation; or
- A first-, second- or third-degree relative has been diagnosed with neurofibromatosis but whose genetic status is unavailable

Or

The member meets at least two of the following criteria:

- six or more light brown spots on the skin ("cafe-au-lait" spots), measuring more than 5 mm in diameter in children or more than 15 mm across in adolescents and adults;
- two or more neurofibromas, or one plexiform neurofibroma (a neurofibroma that involves many nerves);
- freckling in the area of the armpit or the groin;
- two or more growths on the iris of the eye (Lisch nodules or iris hamartomas);
- a tumor on the optic nerve (optic nerve glioma);
- abnormal development of the spine (scoliosis), the temple (sphenoid) bone of the skull or the tibia;
- a parent, sibling or child with NF1

Genetic testing for neurofibromatosis type 2 is medically necessary when the diagnosis is clinically suspected due to signs of disease, but a definitive diagnosis cannot be made without genetic testing. The member must meet one of the following criteria:

- Members with a first degree relative with NF2 (i.e., affected parent, sibling or offspring)
- Multiple spinal tumors (schwannomas, meningiomas)
- Cutaneous schwannomas
- Sporadic vestibular schwannoma less than 30 years of age, or spinal tumor or meningioma less than 20 years of age
- Unilateral vestibular schwannoma in those less than 20 years of age

Rett syndrome:

Genetic testing may be considered medically necessary when:

- The member meets the clinical diagnostic criteria for Rett syndrome; and
- Gene testing is necessary to confirm diagnosis due to clinical uncertainty

Prader-Willi Syndrome

Genetic testing may be considered medically necessary in symptomatic pediatric members for diagnosis of Prader-Willi syndrome or in symptomatic adult members when all of the following criteria are met:

- Documented history of hypotonia and poor suck
- Global developmental delay

Angelman Syndrome

Genetic testing to confirm the absence of maternally expressed gene(s) located on chromosome 15 within bands q11.2 to q13 may be considered medically necessary in symptomatic pediatric members for diagnosis of Angelman Syndrome or in symptomatic adult members when all of the following criteria are met:

- Documentation of absence of major birth defects with normal head circumference
- Evidence of developmental delay by age 6 to 12 months
- Delayed progression and attainment of developmental milestones without overall loss of skills
- Normal metabolic, hematologic and chemical laboratory studies
- Normal brain structure as evidenced by CT or MRI
- Absent or severely impaired speech
- Balance disorder with ataxia or tremulous movement of limbs

Documentation of behavioral characteristics such as inappropriate happy demeanor, frequent and inappropriate laughter or smiling, short attention span, excitability, hand-flapping, or hypermotor activity

Noonan Syndrome:

Genetic testing by via panel may be considered medically necessary when:
The member is suspected of Noonan syndrome due to a combination of **any** of the following:

- A characteristic facial appearance.
- Short stature.
- Heart defect present at birth (congenital heart defect).
- A broad or webbed neck.
- Minor eye problems such as strabismus in up to 95 percent of individuals.
- Bleeding problems such as a history of abnormal bleeding or bruising.
- An unusual chest shape with widely-spaced and low set nipples.
- Developmental delay of varying degrees, but usually mild.
- Undescended testes
- There is a known family history of TPN11, SOS1, RADF1 and KRAS gene mutation

Adult-Onset genetic syndromes

Hereditary Hemochromatosis

1. Genetic testing to confirm a diagnosis of hereditary hemochromatosis should start with HFE genotyping for 3 common variants: C282Y, H63D, S65C.
2. If results are negative, or if carrier status only is identified after testing for three common variants, then sequencing with deletion/duplication analysis with single gene or panel testing, dependent upon clinical presentation, is considered medically necessary for the member.

Genetic testing should be considered medically necessary in individuals with one or more of the following clinical features:

- Serum transferrin saturation >45% at any age
- Serum ferritin concentration value of <300 ng/mL in men and <200 ng/mL in women at any age
- Known family history of hemochromatosis in a first, second or third degree relative
- Known carrier status of HFE-related hemochromatosis in at least one first, second or third degree relative

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL);

Genetic testing to confirm the diagnosis of CADASIL syndrome may be considered medically necessary when:

- Clinical signs, symptoms and imaging results indicate the pre-test probability of CADASIL is moderate to high (total score of 14)*; or
- The diagnosis of CADASIL is inconclusive following alternate methods of testing, including MRI and skin biopsy

Features	***Points***
Migraine	*1*
Migraine with aura	*3*
Psychiatric disturbance	*1*
Transient ischemic attack/stroke	*1 (2 if <50yo)*
Subcortical infarcts	*2*
Cognitive decline	*3*
LE (leukoencephalopathy)	*3*
LE extended to temporal pole	*1*

LE extended to external capsule	*5*

Pooled Frequency of Clinical and Radiologic Features (Pescini et al., 2012)

Charcot-Marie-Tooth:

Genetic Testing for Charcot-Marie-Tooth (CMT) disease is medically necessary when the member has clinical features of CMT and a definitive diagnosis remains uncertain after history, physical examination, genetic counseling and completion of nerve conduction studies and/or electromyography.

- If nerve conduction studies of ulnar/median nerve indicate demyelinating neuropathy (velocity <38 m/s), test for the most commonly identified CMT subtype: CMT1A (PMP22 duplication).
- If the result is negative, multi-gene panel testing of genes GJB1 (CMTX1), MPZ (CMT1B), MFN2 (CMT2A2), LITAF (CMT1C), EGR2 (CMT1D), PMP22 sequencing (CMT1E), GARS (CMT2D), NEFL (CMT2E/1F), GDAP1 (CMT2H/2K) and SH3TC2 (CMT4C).
- If nerve conduction studies of ulnar/median nerve indicate axonal neuropathy (velocity >38 m/s), multi-gene panel testing of genes GJB1 (CMTX1), MPZ (CMT1B), LITAF (CMT1C), EGR2 (CMT1D), PMP22 sequencing (CMT1E), MFN2 (CMT2A2), GARS CMT2D), NEFL (CMT2E/1F), GDAP1 (CMT2H/2K) and SH3TC2 (CMT4C)

Alpha-1-antitrypsin deficiency:

Genetic testing for alpha-1 antitrypsin deficiency may be considered medically necessary when the member meets either criteria 1 or 2, and 3.

Note, genotyping by protease inhibitor (PI) testing (eg isoelectric focusing of serum) should be performed first. Sequencing of *SERPINA1* is only medically necessary when there is a high degree of suspicion for alpha-1 antitrypsin deficiency after negative of inconclusive PI testing.

4. alpha-1 antitrypsin deficiency suspected based on clinical features:
    - COPD, regardless of age or ethnicity
    - Bronchiectasis of unknown etiology; or
    - Chronic liver disease of unknown etiology; or
    - Anti-proteinase 3-positive vasculitis; or
    - Necrotizing panniculitis
    - Neonatal cholestasis
5. Member has a family history of a 1st, 2nd, or 3rd degree relative with alpha-1 antitrypsin deficiency
   AND
6. Member had prior PI testing +/-serum alpha-1 antitrypsin level in the range of severe deficiency

Phenotype	AAT Blood Level
MM	20–53 µM | 150–350 Mg/dL
MZ	12–28 µM | 90–210 Mg/dL
SS	13–27 µM | 100–210 Mg/dL
SZ	10–16 µM | 75–120 Mg/dL
ZZ	2.5–7 µM | 20–45 Mg/dL
NULLNULL	0 µM | 0 Mg/dL

Huntington's disease

Genetic testing for Huntington's disease is recommended when performed as part of a multi-disciplinary team, and is medically necessary in the following scenarios:

1) Diagnostic testing in members with the following symptoms:
    i) Involuntary jerking movements
    ii) Impaired gait, posture and balance
    iii) Dystonia
    iv) Cognitive disorders
2) 1st, 2nd, or 3rd degree biologic relative with a molecular diagnosis of Huntington's disease, or reported clinical diagnosis.

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

Medicaid Business Segment:

Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case-by-case basis.

EXCLUSIONS:

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

Medicaid Business Segment:

Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case by case basis.

The following policies have been reviewed with no change to the policy section. Additional references or background information was added to support the current policy.

MP102 Morphometric Tumor Analysis
MP112 Wireless Capsule Endoscopy
MP163 Thermography
MP175 Trigger Point Injections
MP183 Cranial Electrotherapy Stimulation
MP185 Chemosensitivity and Chemoresistance Assays
MP202 Interferential Stimulation
MP206 Electrocardiographic Body Surface Mapping
MP208 Selective Internal Radiation Therapy
MP221 Suprachoroidal Delivery of Pharmacologic Agents
MP234 Occipital Nerve Stimulation
MP279 Gene Expression Testing to Predict Coronary Artery Disease
MP291 Percutaneous Ultrasonic or Radiofrequency Coblation Tenotomy
MP339 Irreversible Electroporation
MP357 Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer