GENETIC TESTING: EPILEPSY, NEURODEGENERATIVE, AND NEUROMUSCULAR DISORDERS

OVERVIEW

Genetic testing for hereditary epilepsy, neurodegenerative, and neuromuscular disorders may be used to confirm a diagnosis in a patient who has signs and/or symptoms of the disease, but conventional diagnostic methods have been unsuccessful. Confirming the diagnosis may alter some aspects of management and may eliminate the need for further diagnostic workup. This document addresses genetic testing for neurodegenerative and neuromuscular genetic diseases.

POLICY REFERENCE TABLE

Below are a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Ref
Known Familial Variant Analysis for Epilepsy, Neurodegenerative, and Neuromuscular Disorders				
Known Familial Variant Analysis	Targeted Mutation Analysis for a Known Familial Variant	81403, 81326, 81337		
Comprehensive Neuromuscular Disorders Panel				
Comprehensive Neuromuscular Disorders Panel	Comprehensive Neuromuscular Disorders Panel (PerkinElmer Genomics)	81479, 81443	G12, G13, G23-G26, G31, G32, G36, G37	4, 7, 39, 40, 41, 42, 43, 44, 45
	Comprehensive Neuromuscular Panel (PreventionGenetics)			
	Neuromuscular NGS Panel (Sequencing & Deletion/Duplication)			

	(Fulgent Genetics)			
	Neuromuscular Disorders Panel (GeneDx)			
Comprehensive Ataxia Panel				
Comprehensive Ataxia Panel	Genomic Unity Ataxia Repeat Expansion Analysis (Variantyx, Inc.)	0216U	G11.1, G11.19, G11.8, G11.9, Z82.0	17, 38
	Genomic Unity Comprehensive Ataxia Analysis (Variantyx, Inc.)	0217U		
	Comprehensive Spinocerebellar Ataxia Repeat Expansion Panel (MNG Laboratories) Comprehensive Spinocerebellar Ataxia Repeat Expansion Panel, (LabCorp)	81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81343, 81344, 81401, 81479, 81443		
Spinal Muscular Atrophy				
SMN1 Sequencing and/or Deletion/Duplication Analysis	SMN1 Deletion/Duplication Analysis	81329, 81401	G12, Z84.81	9
	Genomic Unity SMN1/2 Analysis (Variantyx Inc)	0236U		
	SMN1 Sequencing Analysis	81336, 81405		
SMN2 Deletion/Duplication Analysis	SMN2 Deletion/Duplication Analysis	81401		
Epilepsy				
Epilepsy Multigene Panel	Childhood-Onset Epilepsy Panel, ARUP Laboratories Infantile-Onset Epilepsy Panel, ARUP Laboratories Infantile Onset Epilepsy Panel, GeneDx Childhood Onset Epilepsy Panel, GeneDx	81401, 81403, 81404, 81405, 81406, 81407, 81419	G40.001-G40.919	8, 12
Alzheimer Disease				

PSEN1, *PSEN2*, and *APP* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	PSEN1 targeted mutation analysis	81405, S3855	F03, G30, G31.1, R41.0, R41.81, Z13.858, Z82.0, Z84.81	2, 5, 6, 50
	PSEN2 targeted mutation analysis	81406		
	APP targeted mutation analysis	81406		
	Early-Onset Alzheimer's Panel, Sequencing (ARUP Laboratories) Early Onset Familial Alzeheimer Disease (EOFAD) NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics) Alzheimer Disease, Familial, Panel (PreventionGenetics)	81405, 81406, S3855		
APOE, *TREM2*, and Others Variant Analysis	APOE Sequencing Analysis APOE Deletion/Duplication Analysis	81401, S3852		
	TREM2 Sequencing Analysis TREM2 Deletion/Duplication Analysis	81479		
Amyotrophic Lateral Sclerosis (ALS)				
ALS Multigene Panel	Amyotrophic lateral sclerosis and related disorders NGS Panel - Comprehensive, (CTGT) Amyotrophic Lateral Sclerosis Panel, (PreventionGenetics)	81404, 81405, 81406, 81479, S3800	G12.21	10, 13, 16
Duchenne and Becker Muscular Dystrophy				
DMD Sequencing and/or Deletion/Duplication Analysis	DMD Deletion/Duplication Analysis	81161	G71.01, R62.59, Z84.81	14, 15, 37
	DMD Sequencing Analysis	81408		
	Genomic Unity DMD Analysis (Variantyx, Inc.)	0218U		
Facioscapulohumeral Muscular Dystrophy (FSHD)				
FSHMD1A deletion/duplication or haplotype analysis, and/or *SMCHD1* and *DNMT3B* sequencing and/or deletion/duplication	FSHMD1A Deletion/Duplication Analysis	81404	G71.02, Z84.81	1, 37, 36, 41
	FSHMD1A Haplotype Analysis	81404		
	SMCHD1 Sequencing SMCHD1 Deletion/Duplication Analysis	81479		
	DNMT3B Sequencing DNMT3B Deletion/Duplication			

analysis or Multigene Panel	Analysis			
	FSHD-(FSHD1 & FSHD2) Detection of Abnormal Alleles with Interpretation - Full Test Panel (University of Iowa Hospitals and Clinics - Department of Pathology)	81404, 81479		
Friedreich's Ataxia				
FXN Repeat Analysis and/or Sequencing Analysis	FXN Repeat Analysis	81284, 81285, 81289, 81401	G11, Z84.81	11, 17
	FXN Sequencing Analysis	81286, 81404		
	Genomic Unity FXN Analysis (Variantyx Inc)	0233U		
Huntington Disease (HD)				
HTT Repeat Analysis	HTT Repeat Analysis	81271, 81274, 81401	G10, Z84.81	10, 18, 19
Inherited Peripheral Neuropathy (Charcot-Marie-Tooth and Hereditary Neuropathy with Liability to Pressure Palsies)				
PMP22 Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	PMP22 Sequencing Analysis PMP22 Deletion/Duplication Analysis	81324, 81325	G60.0, G60.8, G60.9	3, 4, 20, 49
	Charcot-Marie Tooth disease NGS Panel (CTGT) Charcot-Marie Tooth Comprehensive Panel (PreventionGenetics) Hereditary Neuropathy Panel (GeneDx)	81403, 81404, 81405, 81406, 81448, 81479		
Limb-Girdle Muscular Dystrophies (LGMD)				
LGMD Multigene Panel	Limb-Girdle Muscular Dystrophy NGS Panel (CTGT) Limb-Girdle Muscular Panel (GeneDx) Limb-Girdle Muscular Dystrophy (LGMD) Panel (Prevention Genetics) Invitae Limb-Girdle Muscular Dystrophy Panel (Invitae) Limb-Girdle Muscular Dystrophy (MNG Laboratories)	81400, 81404, 81405, 81406, 81408, 81479	G71.0, Z13.71, Z82.0, Z84.81	7
Myotonic Dystrophy				

DMPK and/or *CNBP* Repeat Analysis	DMPK Repeat Analysis	81234, 81239, 81401, 81404, S3853	G71.11, Z84.81	21, 22, 23
	CNBP Repeat Analysis	81187, 81401, S3853		
Hereditary Dystonia				
Dystonia Multigene Panel	Dystonia Panel, GeneDx Dystonia Panel, Prevention Genetics Invitae Dystonia Comprehensive Panel, Invitae	81400, 81404, 81405, 81406, 81443	G24.1, G24.9	25
Parkinson Disease				
GBA, LRRK2, SCNA, and *VPS35* Sequencing and/or Deletion/Duplication Analysis	LRRK2 Sequencing Analysis LRRK2 Deletion/Duplication Analysis	81402, 81408	G20	26, 35
	GBA Sequencing Analysis SCNA Sequencing Analysis VPS35 Sequencing Analysis	81479		
Hereditary Spastic Paraplegia				
Spastic Paraplegia Multigene Panel	Invitae Hereditary Spastic Paraplegia Comprehensive Panel, Invitae Complex Hereditary Spastic Paraplegia Panel, Prevention Genetics Comprehensive Hereditary Spastic Paraplegia Panel, GeneDx	81405, 81406, 81407, 81448, 81479	G11.4, G82.2	27, 28, 29, 30, 31
Congenital Myasthenic Syndrome				
Congenital Myasthenic Multigene Panel	Congenital Myasthenic Syndrome Panel, Prevention Genetics Invitae Congenital Myasthenic Syndrome Panel, Invitae	81443, 81479	G70.2	32
Myotonia Congenita				
CLCN1 Sequencing and/or Deletion/Duplication Analysis	Myotonia Congenita via the *CLCN1* gene, Prevention Genetics	81406	G71.12	33
Hypokalemic Periodic Paralysis				
CACNA1S and *SCN4A*	*CACNA1S* gene analysis	81406, 81479	E87.6, G72.3	34

Sequencing and/or Deletion/Duplication Analysis	*SCN4A* gene analysis			
Other Covered Epilepsy, Neurodegenerative, and Neuromuscular Disorders				
Other Covered Epilepsy, Neuromuscular, and Neurodegenerative Disorders	See list below	81400-81408		46, 47, 48

OTHER RELATED POLICIES

This policy document provides coverage criteria for genetic testing for hereditary neurodegenerative and neuromuscular diseases. Please refer to:

- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing for tests intended to diagnose genetic conditions following amniocentesis, chorionic villus sampling, PUBS, or pregnancy loss.
- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for coverage criteria related to prenatal carrier screening, preimplantation testing of embryos, or preconception carrier screening (including carrier screening for Duchenne/Becker muscular dystrophy and SMA).
- ***Genetic Testing: Pharmacogenetics*** for coverage criteria related to genetic testing prior to the initiation of drug treatment with carbamazepine.
- ***Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders*** for coverage criteria related to genetic testing for mitochondrial disorders.
- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing.
- ***Genetic Testing: Preimplantation Genetic Testing*** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.

- ***Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to epilepsy, neuromuscular, and neurodegenerative disorders not specifically discussed in this or another non-general policy.

COVERAGE CRITERIA

KNOWN FAMILIAL VARIANT ANALYSIS FOR EPILEPSY, NEURODEGENERATIVE, AND NEUROMUSCULAR DISORDERS

I. Targeted mutation analysis for a known familial variant (81403, 81326, 81337) for an epilepsy, neurodegenerative, or neuromuscular disorder is considered **medically necessary** when:

   A. The member has a close relative with a known pathogenic or likely pathogenic variant causing the condition.

II. Targeted mutation analysis for a known familial variant (81403, 81326, 81337) for an epilepsy, neurodegenerative, or neuromuscular disorder is considered **investigational** for all other indications.

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COMPREHENSIVE NEUROMUSCULAR DISORDERS PANEL

I. Comprehensive neuromuscular panel analysis to establish a genetic diagnosis for a neuromuscular disorder (81479, 81443) is considered **medically necessary** when:

   A. The member displays clinical features of a neuromuscular disorder, **AND**

   B. One of the following:

      1. The member is not highly suspected to have a specific neuromuscular disorder for which single-gene analysis (e.g., *SMN1, DMD, PMP22*) would be more appropriate, **OR**

2. The member previously underwent single-gene analysis for a neuromuscular disorder (e.g., *SMN1, DMD, PMP22*) and the results were negative.

II. Comprehensive neuromuscular panel analysis to establish a genetic diagnosis for a neuromuscular disorder (81479, 81443) is considered **investigational** for all other indications.

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COMPREHENSIVE ATAXIA PANEL

I. Comprehensive ataxia panel analysis to establish a genetic diagnosis of an ataxia (81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 0216U, 0217U, 81479, 81443) is considered **medically necessary** when:

A. The member displays one or more of the following clinical features of spinocerebellar ataxia:

1. Progressive incoordination of movement and speech
2. Wide-based, uncoordinated, unsteady gait
3. Muscle stiffness
4. Weakness of the eye muscles (ophthalmoplegia)
5. Dysarthria
6. Eye movement abnormalities (nystagmus, abnormal saccade movements), **AND**

B. Non-genetic causes of ataxia have been ruled out (e.g., alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, primary or metastatic tumors, and paraneoplastic disease associated with occult carcinoma of the ovary, breast, or lung and spinal muscular atrophy).

II. Comprehensive ataxia panel analysis to establish a genetic diagnosis of an ataxia (81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 0216U, 0217U, 81479, 81443) is considered **investigational** for all other indications.

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SPINAL MUSCULAR ATROPHY

SMN1 Sequencing and/or Deletion/Duplication Analysis

I. *SMN1* sequencing (81336, 81405, 0236U) and/or deletion/duplication analysis (81329, 81401) to establish or confirm a diagnosis of Spinal Muscular Atrophy is considered **medically necessary** when:

   A. The member has a positive newborn screen for SMA, **OR**

   B. The member has any of the following clinical features of SMA:

      1. History of motor difficulties, especially with loss of skills
      2. Proximal to distal muscle weakness
      3. Hypotonia
      4. Areflexia/hyporeflexia
      5. Tongue fasciculations
      6. Hand tremor
      7. Recurrent lower respiratory tract infections or severe bronchiolitis in the first few months of life
      8. Evidence of motor unit disease on electromyogram

II. *SMN1* sequencing (81336, 81405, 0236U) and/or deletion/duplication analysis (81329, 81401) to establish or confirm a diagnosis of Spinal Muscular Atrophy is considered **investigational** for all other indications.

SMN2 Deletion/Duplication Analysis

I. *SMN2* deletion/duplication analysis (81401) is considered **medically necessary** when:

   A. The member has a diagnosis of spinal muscular atrophy.

II. *SMN2* deletion/duplication analysis (81401) is considered **investigational** for all other indications.

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EPILEPSY

SCN1A Seizure Disorders and Epilepsy Multigene Panel

I. The use of an epilepsy multigene panel (81419) is considered **medically necessary** when:

   A. The member does not have any metabolic or brain structural abnormalities that predispose to epilepsy, **AND**

   B. The member has any of the following:

      1. Infantile- or early-childhood-onset epilepsy, **OR**
      2. Precipitation of seizure with fever, warmth, or vaccination, **OR**
      3. Prolonged or hemiconvulsive seizures, **OR**
      4. Seizure provocation with overstimulation or flashing/patterned visual stimulus, **OR**
      5. Worsening of seizures with medications that inhibit sodium channel function as the primary mechanism of action (e.g., carbamazepine, oxcarbazepine, phenytoin, lamotrigine).

II. The use of an epilepsy multigene panel (81419) is considered **investigational** for all other indications.

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ALZHEIMER DISEASE

PSEN1, *PSEN2*, and *APP* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel

I. *PSEN1* (81405, S3855), *PSEN2* (81406), and/or *APP* (81406) sequencing and/or deletion/duplication analysis (S3855, 81405, 81406) or multigene panel (S3855, 81405, 81406) to establish a diagnosis or determine future risk to develop early-onset Alzheimer disease is considered **medically necessary** when:

   A. The member is 18 years of age or older, **AND**

   B. The member is asymptomatic*, **AND**

      1. The member has a close relative with a known early-onset Alzheimer disease-causing mutation in *PSEN1*, *PSEN2*, or *APP*, **OR**

      2. The member has an apparently autosomal dominant family history of dementia with one or more cases of early onset Alzheimer disease, **OR**

   C. The member is symptomatic, **AND**

      1. Has a diagnosis of dementia ≤65 years of age, **AND**

         a) The member has a close relative diagnosed with dementia, **OR**

         b) An unknown family history (e.g., adoption).

II. *PSEN1* (81405, S3855), *PSEN2* (81406), and/or *APP* (81406) sequencing and/or deletion/duplication analysis (S3855, 81405, 81406) to establish the diagnosis or determine future risk to develop early-onset Alzheimer disease is considered **investigational** for all other indications.

APOE, *TREM2* and Others Variant Analysis

I. Genetic testing to establish a diagnosis or determine future risk to develop Alzheimer disease via other genes, including but not limited to, *APOE* (81401 S3852) or *TREM2* (81479) is considered **investigational**.

* Predictive testing should only be performed in the setting and context of thorough pre- and post-test counseling

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AMYOTROPHIC LATERAL SCLEROSIS (ALS)

ALS Multigene Panel Analysis

I. Multigene panel analysis to establish a genetic etiology of amyotrophic lateral sclerosis (ALS) (81404, 81405, 81406, 81479, S3800) is considered **medically necessary** when:

   A. The member is 18 years of age or older, **AND**

   B. The member displays all of the following clinical features of ALS:

      1. Evidence of lower motor neuron (LMN) degeneration, **AND**

      2. Evidence of upper motor neuron (UMN) degeneration, **AND**

      3. Progressive spread of symptoms, **AND**

      4. No evidence of other disease processes that could explain the LMN and UMN degeneration, **AND**

   C. The panel includes, at a minimum, the following genes: *C9orf72*, *SOD1*, *FUS*, and *TARDBP*.

II. Multigene panel analysis to establish a genetic etiology of amyotrophic lateral sclerosis (ALS) (81404, 81405, 81406, 81479, S3800) is considered **investigational** for all other indications.

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DUCHENNE AND BECKER MUSCULAR DYSTROPHY

DMD Sequencing and/or Deletion/Duplication Analysis

I. *DMD* sequencing and/or deletion/duplication analysis (81161, 81408, 0218U) to establish or confirm a diagnosis of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) is considered **medically necessary** when:

A. The member is a male, **AND**

1. The member meets one of the following:

a) All of the following clinical findings of DMD:

(1) Progressive symmetric muscular weakness - proximal greater than distal, often with calf hypertrophy (enlargement)

(2) Symptoms presenting before age five years

(3) Wheelchair dependency before age 13 years

(4) Serum creatine kinase concentration more than 10 times the normal levels, **OR**

b) Any of the following clinical findings of BMD:

(1) Progressive symmetric muscle weakness (proximal > distal) often with calf hypertrophy; weakness of quadriceps femoris in some cases the only sign

(2) Activity-induced cramping

(3) Flexion contractures of the elbows

(4) Wheelchair dependency (after age 16 years)

(5) Preservation of neck flexor muscle strength, **OR**

2. The member is asymptomatic, **AND**

a) Has a biological sibling with a clinical and/or molecular diagnosis of Duchenne or Becker muscular dystrophy, **OR**

b) Has a biological mother that is an obligate carrier for Duchenne or Becker muscular dystrophy, **OR**

B. The member is a female, **AND**

1. Has a first- or second-degree relative with a clinical diagnosis of Duchenne or Becker muscular dystrophy.

II. *DMD* sequencing and/or deletion/duplication analysis (81161, 81408, 0218U) to establish a diagnosis of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) is considered **investigational** for all other indications.

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FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

FSHMD1A Deletion/duplication or Haplotype Analysis, and/or *SMCHD1* and *DNMT3B* Sequencing and/or Deletion/duplication Analysis or Multigene Panel

I. *FSHMD1A* deletion/duplication or haplotype analysis (81404), and/or *SMCHD1* (81404, 81479) and *DNMT3B* sequencing and/or deletion/duplication analysis (81479) or multigene panel analysis (81404, 81479) to establish or confirm a diagnosis of facioscapulohumeral muscular dystrophy is considered **medically necessary** when:

A. The member displays any of the following clinical features of FSHD:

1. Weakness (which is often asymmetric) that predominantly involves the facial, scapular stabilizer, or foot dorsiflexor muscles without associated ocular or bulbar muscle weakness.

2. Progression of weakness after pregnancy

3. Prior diagnosis of FSHD with inflammatory myopathy that was refractory to immunosuppression.

II. *FSHMD1A* deletion/duplication or haplotype analysis (81404), and/or *SMCHD1* (81404, 81479) and *DNMT3B* sequencing and/or deletion/duplication analysis (81479) or multigene panel analysis (81404, 81479) to establish or confirm a diagnosis of facioscapulohumeral muscular dystrophy is considered **investigational** for all other indications.

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FRIEDREICH'S ATAXIA

FXN Repeat Analysis

I. *FXN* repeat analysis (81284, 81285, 81289, 81401) or sequencing analysis (81286, 81404, 0233U) to establish or confirm a diagnosis of Friedreich's Ataxia is considered **medically necessary** when:

   A. The member is asymptomatic, **AND**

      1. The member has a biological sibling diagnosed with Friedreich's ataxia, **OR**

   B. The member meets both of the following:

      1. The member has been diagnosed with cerebellar ataxia, **AND**

      2. Non-genetic causes for the ataxia have been ruled out (e.g., alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, tumors).

II. *FXN* repeat analysis (81284, 81285, 81289, 81401) and sequencing analysis (81286, 81404, 0233U) to establish or confirm a diagnosis of Friedreich's Ataxia is considered **investigational** for all other indications.

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HUNTINGTON DISEASE

HTT Repeat Analysis

I. Genetic testing of *HTT* repeat analysis to establish a diagnosis or for predictive testing of Huntington's disease (HD) (81271, 81274, 81401) is considered **medically necessary** when:

A. The member displays at least two of the following clinical features of Huntington disease:

1. Progressive motor disability featuring chorea and gait disturbance
2. Mental disturbances including:

a) Cognitive decline

b) Changes in personality

c) Depression, **OR**

B. The member is undergoing predictive testing*, **AND**

1. The member is presymptomatic/asymptomatic, **AND**

a) The member has a close relative with CAG trinucleotide repeat expansion of 27 or more in *HTT*, **OR**

b) The member has a first-degree relative with a clinical diagnosis of HD without prior genetic testing.

II. Genetic testing of *HTT* repeat analysis to establish a diagnosis or for predictive testing of Huntington's disease (HD) (81271, 81274, 81401) is considered **investigational** for all other indications.

* Predictive testing should only be performed in the setting and context of thorough pre- and post-test counseling.

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INHERITED PERIPHERAL NEUROPATHIES
(e.g.,CHARCOT-MARIE-TOOTH DISEASE AND HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES)

PMP22 Sequencing and/or Deletion/Duplication or Multigene Panel

I. PMP22 Sequencing and/or Deletion/Duplication analysis (81324, 81325) or multigene panel analysis to establish a genetic diagnosis of an inherited peripheral neuropathy (81403, 81404, 81405, 81406, 81448, 81479) is considered **medically necessary** when:

   A. The member displays one or more of the following clinical features of an inherited motor or sensory peripheral neuropathy, but otherwise does not have a diagnosis of CMT or HNPP:

      1. Distal muscle weakness and atrophy, sensory loss, and, **OR**
      2. Pes cavus foot deformity, **OR**
      3. Weak ankle dorsiflexion, **OR**
      4. Depressed tendon reflexes, **OR**
      5. Recurrent acute focal sensory and motor neuropathies mainly at entrapment sites, **OR**
      6. Painless nerve palsy after minor trauma or compression, **OR**
      7. Complete spontaneous recovery from neuropathies, **OR**

   B. The member is asymptomatic, **AND**

   C. Has a close relative diagnosed with an inherited peripheral neuropathy whose genetic status is unavailable, **AND**

   D. The panel includes at a minimum all of the following genes: PMP22 by duplication analysis, GDAP1, GJB1, HINT1, MFN2, MPZ, SH3TC2, SORD.

II. PMP22 Sequencing and/or Deletion/Duplication analysis (81324, 81325) or multigene panel analysis to establish a genetic diagnosis of an inherited

peripheral neuropathy (81403, 81404, 81405, 81406, 81448, 81479) is considered **investigational** for all other indications.

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LIMB-GIRDLE MUSCULAR DYSTROPHY (LGMD)

Limb-girdle Muscular Dystrophy Multigene Panel

I. Multigene panel analysis to establish a diagnosis of limb-girdle muscular dystrophy (81400, 81404, 81405, 81406, 81408, 81479) is considered **medically necessary** when:

   A. The member displays any of the following clinical features of limb-girdle muscular dystrophy:

      1. Gradually progressive muscle weakness involving predominantly the proximal arms and legs, with normal sensory exam (distal muscles are involved, but usually to a lesser extent)

      2. Elevated creatine kinase level, **OR**

   B. The member is asymptomatic, **AND**

      1. Has a close relative diagnosed with limb-girdle muscular dystrophy whose genetic status is unavailable.

II. Multigene panel analysis to establish a diagnosis of limb-girdle muscular dystrophy (81400, 81404, 81405, 81406, 81408, 81479) is considered **investigational** for all other indications.

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MYOTONIC DYSTROPHY

DMPK and/or *CNBP* (*ZNF9*) Repeat Analysis

I. *DMPK* repeat analysis (81234, 81239, 81401, 81404, S3853) and/or *CNBP* (*ZNF9*) repeat analysis (81187, 81401, S3853) to establish a diagnosis of myotonic dystrophy is considered **medically necessary** when:

A. The member meets either of the following:

1. The member is a neonate with two or more of the following:

a) Hypotonia

b) Facial muscle weakness

c) Generalized weakness

d) Positional malformations, including clubfoot

e) Respiratory insufficiency, **OR**

2. The member is any age and displays any of the following clinical features of myotonic dystrophy:

a) Muscle weakness, especially of the distal leg, hand, neck, and face

b) Myotonia, which often manifests as the inability to quickly release a hand grip (grip myotonia)

c) Posterior subcapsular cataracts

d) Cardiac conduction defects or progressive cardiomyopathy

e) Insulin sensitivity

f) Hypogammaglobulinemia, **OR**

B. The member is asymptomatic, **AND**

1. The member is 18 years of age or older, **AND**

2. The member has a first-degree relative with Myotonic dystrophy type 1 or 2.

II. *DMPK* repeat analysis (81234, 81239, 81401, 81404, S3853) and *CNBP* (*ZNF9*) repeat analysis (81187, 81401, S3853) to establish a diagnosis of myotonic dystrophy is considered **investigational** for all other indications.

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HEREDITARY DYSTONIA

Hereditary Dystonia Multigene Panel

I. Multigene panel analysis to establish a genetic diagnosis of hereditary dystonia (81400, 81404, 81405, 81406, 81443) is considered **medically necessary** when:

   A. The member has all of the following clinical features of a hereditary dystonia:

      1. Sustained or intermittent muscle contractions

      2. Abnormal or repetitive movements and/or postures

      3. The dystonia is initiated or worsened by voluntary action

II. Multigene panel analysis to establish a genetic diagnosis of hereditary dystonia (81400, 81404, 81405, 81406, 81443) is considered **investigational** for all other indications.

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PARKINSON DISEASE

GBA, *LRRK2*, *SNCA*, and *VPS35* Sequencing and/or Deletion/Duplication Analysis

I. *GBA* (81479), *LRRK2* (81402, 81408), *SNCA* (81479) and *VPS35* (81479) sequencing and/or deletion/duplication analysis to establish a genetic diagnosis of Parkinson disease is considered **medically necessary** when:

   A. The member has a diagnosis of Parkinson disease, **AND**

   B. The member has two or more first-degree or second-degree relatives who have been diagnosed with Parkinson disease.

II. *GBA* (81479), *LRRK2* (81402, 81408), *SNCA* (81479) and *VPS35* (81479) sequencing and/or deletion/duplication analysis to establish a genetic diagnosis of Parkinson disease is considered **investigational** for all other indications.

III. All other genetic testing to establish a genetic diagnosis of Parkinson disease is considered **investigational**.

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HEREDITARY SPASTIC PARAPLEGIA

Hereditary Spastic Paraplegia Multigene Panel

I. Multigene panel analysis to establish a genetic diagnosis of hereditary spastic paraplegia (81405, 81406, 81407, 81448, 81479) is considered **medically necessary** when:

   A. The member has any of the following:

      1. lower-extremity spasticity especially in hamstrings, quadriceps, adductors, and gastrocnemius-soleus muscles, **OR**

      2. Weakness especially in the iliopsoas, hamstring, and tibialis anterior, **OR**

3. Lower-extremity hyperreflexia and extensor plantar responses, **OR**
4. Mildly impaired vibration sensation in the distal lower extremities.

B. A multigene panel must include the following genes, at a minimum: SPG4, SPG3A, SPG30, SPG5A, SPG7, SPG11.

II. Multigene panel analysis to establish a genetic diagnosis of hereditary spastic paraplegia (81405, 81406, 81407, 81448, 81479) is considered **investigational** for all other indications.

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CONGENITAL MYASTHENIC SYNDROMES

Congenital Myasthenic Syndromes Multigene Panel

I. Multigene panel analysis to establish a genetic diagnosis of congenital myasthenic syndromes (81479) is considered **medically necessary** when:

A. The member has a history of fatigable weakness involving ocular, bulbar, and limb muscles with onset at or shortly after birth or in early childhood, **AND**

B. A decremental EMG response of the compound muscle action potential (CMAP) on low-frequency (2-3 Hz) stimulation, **AND**

C. A positive response to acetylcholinesterase (AchE) inhibitors, **AND**

D. Absence of anti-acetylcholine receptor (anti-AChR) and anti-MuSK antibodies in the serum, **AND**

E. Lack of improvement of clinical symptoms with immunosuppressive therapy, **AND**

F. Absence of major pathology in a skeletal muscle biopsy specimen despite considerable muscle weakness.

II. Multigene panel analysis to establish a genetic diagnosis of congenital myasthenic syndromes (81479) is considered **investigational** for all other indications.

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MYOTONIA CONGENITA

CLCN1 Sequencing and/or Deletion/Duplication Analysis

I. *CLCN1* sequencing and/or deletion/duplication analysis (81406) to establish a genetic diagnosis of myotonia congenita is considered **medically necessary** when:

   A. The member has episodes of muscle stiffness (myotonia*) or cramps beginning in early childhood which is alleviated by brief exercise, **AND**

   B. Myotonic contraction is elicited by percussion of muscles, **AND**

   C. Serum creatine kinase concentration that may be slightly elevated (≤3-4x the upper limits of normal), **AND**

   D. Electromyography (EMG) performed with needle electrodes discloses characteristic showers of spontaneous electrical activity (myotonic bursts).

II. *CLCN1* sequencing and/or deletion/duplication analysis (81406) to establish a genetic diagnosis of myotonia congenita is considered **investigational** for all other indications.

*Myotonia is defined as impaired relaxation of skeletal muscle after voluntary contraction.

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HYPOKALEMIC PERIODIC PARALYSIS

CACNA1S and *SCN4A* Sequencing and/or Deletion/Duplication Analysis

I. *CACNA1S* and *SCN4A* sequencing and/or deletion/duplication analysis (81406, 81479) to establish a genetic diagnosis of periodic paralysis is considered **medically necessary** when:

A. The member has had two or more attacks of muscle weakness with documented serum potassium <3.5 mEq/L, **OR**

B. The member has had one attack of muscle weakness, **AND**

   1. Has a close relative who has had one attack of muscle weakness in with documented serum potassium <3.5 mEq/L, **OR**

C. The member has three or more of the following features:

   1. Onset of symptoms in the first or second decade, **OR**

   2. Muscle weakness involving ≥1 limbs lasting longer than two hours, **OR**

   3. The presence of triggers (previous carbohydrate rich meal, symptom onset during rest after exercise, stress), **OR**

   4. Improvement in symptoms with potassium intake, **OR**

   5. A family history of a clinical or genetic diagnosis of hypokalemic periodic paralysis in a close relative, **OR**

   6. Positive long exercise test, **AND**

D. Alternative causes of hypokalemia have been excluded (e.g., renal, adrenal, thyroid dysfunction; renal tubular acidosis; diuretic and laxative abuse).

II. *CACNA1S* and *SCN4A* sequencing and/or deletion/duplication analysis (81406, 81479) to establish a genetic diagnosis of periodic paralysis is considered **investigational** for all other indications.

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OTHER COVERED EPILEPSY, NEUROMUSCULAR, AND NEURODEGENERATIVE DISORDERS

I. Genetic testing to establish or confirm one of the following epilepsy, neuromuscular, and neurodegenerative conditions to guide management is considered **medically necessary** when the member demonstrates clinical

features* consistent with the disorder (the list is not meant to be comprehensive, see II below):

A. Hereditary Transthyretin Amyloidosis
B. X-linked Adrenoleukodystrophy
C. L1 Syndrome
D. SCN9A Neuropathic Pain Syndromes
E. Cerebral Cavernous Malformation, Familial
F. STAC3 Disorder

II. Genetic testing to establish or confirm the diagnosis of all other epilepsy, neurodegenerative, and neuromuscular disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *General Approach to Genetic Testing* (see policy for coverage criteria).

*Clinical features for a specific disorder may be outlined in resources such as GeneReviews, OMIM, National Library of Medicine, Genetics Home Reference, or other scholarly source.

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NOTES/DEFINITIONS

1. **Close relatives** include first, second, and third degree blood relatives on the same side of the family:
    a. **First-degree relatives** are parents, siblings, and children
    b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
    c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins
2. **Infantile- or early-childhood-onset epilepsy** are disorders in which epilepsy is the core clinical symptom. These include: Dravet syndrome, early infantile epileptic encephalopathy, generalized epilepsy with febrile seizures plus, epilepsy and intellectual disability limited to females, nocturnal frontal lobe epilepsy. Neonatal onset is before 44 weeks of gestational age, while infantile onset is before 1 year of age.

3. **Early onset Alzheimer disease** is defined as Alzheimer disease occurring in an individual under age 65
4. A **neonate** is a baby who is four weeks old or younger
5. A **minor** is any person under the age of 18.
6. **Childhood** is the period of development until the 18th birthday.

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BACKGROUND AND RATIONALE

Practice Guidelines and Position Statements

American Academy of Neurology

Genetic Testing for Inherited Peripheral Neuropathies

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 and recommended that genetic testing is established as useful for the accurate diagnosis and classification of hereditary neuropathies.

Genetic Testing for Epilepsy

The American Academy of Neurology and Child Neurology Society published joint guidelines (2006) which were reviewed and reaffirmed in 2016. The guidelines stated that there is insufficient evidence to support or refute whether genetic testing should be done routinely.

Genetic Testing for Facioscapulohumeral Muscular Dystrophy

The American Academy of Neurology and American Association of Neuromuscular & Electrodiagnostic Medicine guidelines (2015) on FSHD state that genetic testing can confirm the diagnosis in many patients with FSHD type 1 and further state that if the patient tests negative for the D4Z4 contraction, testing for FSHD type 2 or other myopathies can be done.

Genetic Testing for Limb-Girdle Muscular Dystrophy

The American Academy of Neurology and the American Association of Neuromuscular and Electrodiagnostic Medicine (2014) issued evidenced-based guidelines for the diagnosis and treatment of limb-girdle and distal dystrophies. These guidelines recommend that "For patients with suspected muscular dystrophy, clinicians should use a clinical approach to guide genetic diagnosis based on the clinical phenotype, including the pattern of muscle involvement, inheritance pattern, age at onset, and associated manifestations (e.g., early contractures, cardiac or respiratory involvement) (Level B). In patients with suspected muscular dystrophy in whom initial clinically directed genetic testing does not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole-genome screening, or next-generation sequencing to identify the genetic abnormality (Level C)."

Genetic Testing for Alzheimer Disease

The American Academy of Neurology (2001) made the guideline recommendations that routine use of *APOE* genotyping in patients with suspected AD is not recommended.

American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM)

The AANEM developed a position statement regarding the clinical usefulness of genetic testing in the diagnosis of neuromuscular disease (2016) generally supporting the use of genetic testing in the diagnosis of neuromuscular disorders, which made the following summary statement:

> "The AANEM believes that genetic testing and arriving at a specific molecular diagnosis is critical to providing high quality care to NM patients. Many recommendations and guidelines exist to direct the rational selection of appropriate genetic testing. The cost of testing should not be a deterrent, since there are important clinical, safety, psychosocial, and research benefits to genetic testing in NM disease."

American Academy of Family Physicians

Genetic Testing for Inherited Peripheral Neuropathies

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.

American College of Medical Genetics and National Society of Genetic Counselors

Genetic Testing for Alzheimer Disease

The American College of Medical Genetics jointly with the National Society of Genetic Counselors (2011) issued joint practice guidelines, which have since been reaffirmed and reclassified as a practice resource (2019). These guidelines state that:

- Pediatric testing for AD should not occur.
- Prenatal testing for AD is not advised if the patient intends to continue a pregnancy with a mutation.
- Testing for genes associated with early-onset autosomal dominant AD should be offered in the following situations:
    - A symptomatic individual with EOAD in the setting of a family history of dementia or the setting of an unknown family history (eg, adoption).
    - Autosomal dominant family history of dementia with one or more cases of EOAD.
    - A relative with a mutation consistent with EOAD (currently *PSEN1/2* or *APP*).

The American College of Medical Genetics and Genomics has listed genetic testing for apolipoprotein E (*APOE*) alleles as 1 of 5 recommendations in the Choosing Wisely initiative. The recommendation is “Don’t order APOE genetic testing as a predictive test for Alzheimer disease.” The stated rationale is that *APOE* is a susceptibility gene for late-onset Alzheimer disease (AD), the most common cause of dementia: “The presence of an ε4 allele is neither necessary nor sufficient to cause AD. The relative risk conferred by the ε4 allele is confounded by the presence of other risk alleles, gender, environment and possibly ethnicity, and the APOE genotyping for AD risk prediction has limited clinical utility and poor predictive value.”

American College of Medical Genetics

Genetic Testing for Hereditary Ataxias

ACMG (2013) stated the following in regard to “establishing the diagnosis of hereditary ataxia:

1. Detection on neurological examination of typical clinical signs including poorly coordinated gait and finger/hand movements, dysarthria (incoordination of speech), and eye movement abnormalities such as nystagmus, abnormal saccade movements, and ophthalmoplegia.
2. Exclusion of nongenetic causes of ataxia.

3. Documentation of the hereditary nature of the disease by finding a positive family history of ataxia, identifying an ataxia-causing mutation, or recognizing a clinical phenotype characteristic of a genetic form of ataxia."

"Differential diagnosis of hereditary ataxia includes acquired, nongenetic causes of ataxia, such as alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, primary or metastatic tumors, and paraneoplastic diseases associated with occult carcinoma of the ovary, breast, or lung, and the idiopathic degenerative disease multiple system atrophy (spinal muscular atrophy). The possibility of an acquired cause of ataxia needs to be considered in each individual with ataxia because a specific treatment may be available."

National Society of Genetic Counselors

The National Society of Genetic Counselors updated a position statement (2017) regarding the genetic testing of minors for adult-onset conditions, stating the following:

> "[NSGC] encourages deferring predictive genetic testing of minors for adult-onset conditions when results will not impact childhood medical management or significantly benefit the child. Predictive testing should optimally be deferred until the individual has the capacity to weigh the associated risks, benefits, and limitations of this information, taking his/her circumstances, preferences, and beliefs into account to preserve his/her autonomy and right to an open future."

International League Against Epilepsy

Genetic Testing for Epilepsy

In 2015, the International League Against Epilepsy issued a report with recommendations on the management of infantile seizures, which included the following related to genetic testing in epilepsy:

- Genetic screening should not be undertaken at primary or secondary level care (expert opinion).
- Standard care should permit genetic counseling by trained personnel at all levels of care (expert opinion).
- Genetic evaluation for Dravet syndrome, and other infantile-onset epileptic encephalopathies, should be available in tertiary care (weak evidence, level C recommendation).

American Academy of Pediatrics (AAP)

Genetic Testing for Duchenne and Becker Muscular Dystrophy

The AAP (2005, reaffirmed in 2008) published the following recommendations for cardiac care in carriers of DMD or BMD:

- Carriers of DMD or BMD should be made aware of the risk of developing cardiomyopathy and educated about the signs and symptoms of heart failure.
- Carriers of DMD or BMD should be referred for evaluation by a cardiac specialist with experience in the treatment of heart failure and/or neuromuscular disorders. Patients should undergo initial complete cardiac evaluation in late adolescence or early adulthood or at the onset of cardiac signs and symptoms, if these signs or symptoms appear earlier.
- Carriers should be screened with a complete cardiac evaluation at a minimum of every 5 years starting at 25 to 30 years of age.
- Treatment of cardiac disease is similar to that outlined for boys with DMD or BMD.

DMD Care Considerations Working Group

Genetic Testing for Duchenne and Becker Muscular Dystrophy

The DMD Care Considerations Working Group (2018), selected by the CDC, created guidelines for the diagnosis and management of DMD, stating the following:

> "Because approximately 70% of individuals with DMD have a single-exon or multi-exon deletion or duplication in the dystrophin gene, dystrophin gene deletion and duplication testing is usually the first confirmatory test. Testing is best done by multiplex ligation dependent probe amplification (MLPA) or comparative genomic hybridisation array, since use of multiplex PCR can only identify deletions. Identification of the boundaries of a deletion or duplication mutation by MLPA or comparative genomic hybridisation array might indicate whether the mutation is predicted to preserve or disrupt the reading frame. If deletion or duplication testing is negative, genetic sequencing should be done to screen for the remaining types of mutations that are attributed to DMD (approximately 25–30%). These mutations include point mutations (nonsense or missense), small deletions, and small duplications or insertions, which can be identified using next-generation sequencing. Finally, if genetic testing does not confirm a clinical diagnosis of DMD, then a muscle biopsy sample should be tested for the presence

> of dystrophin protein by immunohistochemistry of tissue cryosections or by western blot of a muscle protein extract."

Myotonic Dystrophy Foundation

Genetic Testing for Myotonic Dystrophy Type 1

More than 65 leading myotonic dystrophy (DM) clinicians in Western Europe, the UK, Canada and the US joined in a process started in Spring 2015 and concluded in Spring 2017 to create the Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 1, which included this recommendation for genetic testing:

> "DM1 via molecular genetic testing as the first line of investigation for any patient suspected of having DM1. Muscle biopsy should no longer be performed as a diagnostic test when there is clear clinical suspicion of DM1. Patients with more than 50 CTG repeats in the 3' untranslated region of the DMPK gene on chromosome 19 are considered to have DM1. False-negative genetic testing results can occur, even in a family with an established DM1 diagnosis; expert referral is recommended."

Genetic Testing for Myotonic Dystrophy Type 2

15 leading myotonic dystrophy (DM) clinicians from western Europe, Canada and the United States have created the Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 2, which included this recommendation for genetic testing:

> "DM2 via DNA-based genetic testing as the first line of investigation for any patient suspected of having DM2. When there is clear clinical suspicion of DM2, muscle biopsy should no longer be performed as a diagnostic test. Patients with more than 75 CCTG in intron 1 of the CNBP gene in chromosome 3q21.3 can be considered to have DM2. Patients with repeats in the 28-75 range gray zone are unclear. DM2 repeat sizing in tissues other than blood and/or segregation studies in the family may be valuable in addressing potential pathogenicity. False-negative genetic testing results can occur, even in a family with an established DM2 diagnosis. Expert referral is recommended."

American Academy of Pediatrics (AAP) and American College of Medical Genetics and Genomics (ACMG)

> "Decisions about whether to offer genetic testing and screening should be driven

by the best interest of the child."

"The AAP and the ACMG do not support routine carrier testing or screening for recessive conditions when carrier status has no medical relevance during minority."

"Predictive genetic testing for adult onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality."

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