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 Panel (PreventionGenetics)	81161, 81404, 81405, 81406, 81479	G12, G13, G23-G26, G31, G32, G36, G37	25, 26
	Neuromuscular NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics)	81407, 81408, 81479		

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Ref
	Neuromuscular Disorders Panel (GeneDx)	81405, 81406, 81407, 81408		
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	14
	Genomic Unity Comprehensive Ataxia Analysis (Variantyx, Inc.)	0217U		
	Ataxia Xpanded Panel (GeneDx)	81185, 81186, 81403, 81404, 81405, 81406, 81407, 81408		
	Ataxia Panel (Blueprint Genetics)	81286, 81189, 81404, 81406, 81407, 81408, 81479, 81460, 81465		
Spinal Muscular Atrophy				
SMN1 Sequencing and/or Deletion/Duplication Analysis	Spinal Muscular Atrophy (SMA) (LabCorp)	81329	G12, Z84.81	7
	Genomic Unity SMN1/2 Analysis (Variantyx Inc.)	0236U		
	Spinal Muscular Atrophy Screen (NxGen MDx)	81336		
SMN2 Deletion/Duplication Analysis	SMN2 Copy Number Determination (PerkinElmer)	81329		
Epilepsy				
SCN1A Seizure Disorders and Epilepsy Multigene Panel	Childhood-Onset Epilepsy Panel, Sequencing and Deletion/Duplication (ARUP Laboratories)	81189, 81404, 81405, 81406, 81407	G40.001-G40.919	31, 32
	Infantile Epilepsy Panel, Sequencing Analysis and Exon-Level Deletion/Duplication (ARUP	81185, 81404, 81405, 81406, 81407		

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Ref
	Laboratories)			
	Infantile Epilepsy Panel (GeneDx)	81404, 81405, 81406, 81407		
	Childhood-Onset Epilepsy Panel (GeneDx)			
	Invitae Epilepsy Panel (Invitae)	81419		
Alzheimer Disease				
PSEN1, *PSEN2*, and *APP* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	*PSEN1* Full Gene Sequencing and Deletion/Duplication (Invitae)	81405, 81479	F03, G30, G31.1, R41.0, R41.81, Z13.858, Z82.0, Z84.81	2, 4, 5, 30
	Alzheimer's Disease, Familial via the *PSEN2* Gene (PreventionGenetics)	81406, 81479		
	APP Full Gene Sequencing and Deletion/Duplication (Invitae)	81406, 81479		
	Alzheimer Disease, Familial, Panel (PreventionGenetics)	81405, 81406, 81479		
	Hereditary Alzheimer's Disease Panel (Invitae)			
APOE, *TREM2*, and Others Variant Analysis	*APOE* Single Gene Test (Blueprint Genetics)	81401, 81479		
	TREM2 Full Gene Sequencing and Deletion/Duplication (Invitae)	81479		
Amyotrophic Lateral Sclerosis (ALS)				
Familial Amyotrophic Lateral Sclerosis (FALS) Panel	Amyotrophic Lateral Sclerosis (ALS) Panel (PreventionGenetics)	81179, 81403, 81404, 81405, 81406, 81479	G12.21	8, 10, 13
	Amyotrophic Lateral Sclerosis Panel - Primary Genes (Invitae)	81406, 81407, 81479		
Duchenne and Becker Muscular Dystrophy				
DMD Sequencing and/or Deletion/Duplication Analysis	Duchenne/Becker MD (DMD) Del/Dup (GeneDx)	81161	G71.01, R62.59, Z84.81	11, 12
	Duchenne/Becker MD (DMD) Gene Sequencing (GeneDx)	81408		

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Ref
Facioscapulohumeral Muscular Dystrophy (FSHD)				
FSHD1 deletion/duplication or haplotype analysis, and/or *SMCHD1* and *DNMT3B* sequencing and/or deletion/duplication analysis or Multigene Panel	*FSHD1* Southern Blot Test (Quest Diagnostics)	81404	G71.02, Z84.81	1
	FSHD-(FSHD1 & FSHD2) Detection of Abnormal Alleles with Interpretation - 4qA/4qB Haplotyping (University of Iowa Hospitals and Clinics - Department of Pathology)	81404		
	Facioscapulohumeral Muscular Dystrophy 2 via the SMCHD1 Gene (PreventionGenetics)	81479		
	DNMT3B Full Gene Sequencing And Deletion/Duplication (Invitae)			
	FSHD-(FSHD1 & FSHD2) Detection of Abnormal Alleles with Interpretation(University of Iowa Hospitals and Clinics - Department of Pathology)	81404		
Friedreich's Ataxia				
FXN Repeat Analysis and/or Sequencing Analysis	Friedreich Ataxia (FXN) Repeat Expansion Test (Athena Diagnostics)	81284	G11, Z84.81	9, 14
	Friedreich Ataxia Sequencing and Del/Dup (GeneDx)	81286		
Huntington Disease (HD)				
HTT Repeat Analysis	Huntington Disease Mutation Analysis (Quest Diagnostics)	81271	G10, Z84.81	15
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* Duplication/Deletion Test (Athena Diagnostics)	81324	G60.0, G60.8, G60.9	3, 16
	PMP22 Gene Sequencing (GeneDx)	81325		

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Ref
	Charcot-Marie Tooth (CMT) - Comprehensive Panel (PreventionGenetics)	81324, 81325, 81403, 81404, 81405, 81406, 81479		
	Charcot-Marie-Tooth Panel (GeneDx)	81448		
Limb-Girdle Muscular Dystrophies (LGMD)				
LGMD Multigene Panel	Limb-Girdle Muscular Panel (GeneDx)	81405, 81406, 81408	G71.0, Z13.71, Z82.0, Z84.81	6
	Limb-Girdle Muscular Dystrophy Panel (Invitae)	81161, 81404, 81405, 81406, 81479		
Myotonic Dystrophy				
DMPK and/or *CNBP* Repeat Analysis	*DMPK* Repeat Analysis (GeneDx)	81234	G71.11, Z84.81	17, 18
	DMPK DNA Test (DM1) (Athena Diagnostics)			
	CNBP Repeat Analysis (GeneDx)	81187		
Hereditary Dystonia				
Dystonia Multigene Panel	Dystonia Panel (GeneDx)	81404, 81405, 81406, 81407, 81408	G24.1, G24.9	19
	Dystonia Panel (PreventionGenetics)	81404, 81405, 81406, 81479		
	Dystonia Comprehensive Panel (Invitae)	81405, 81406, 81407, 81479		
Parkinson Disease				
GBA, *LRRK2*, *SCNA*, and *VPS35* Sequencing and/or Deletion/Duplication Analysis	Parkinson Disease via the *LRRK2* Gene (PreventionGenetics)	81408, 81479	G20	20, 24
	Gaucher Disease via the *GBA* Gene (PreventionGenetics)	81479		
	Parkinson's Disease via the *SCNA* Gene (PreventionGenetics)			

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Ref
	VPS35 Full Gene Sequencing and Deletion/Duplication (Invitae)			
Hereditary Spastic Paraplegia				
Spastic Paraplegia Multigene Panel	Comprehensive Hereditary Spastic Paraplegia Panel (GeneDx)	81404, 81405, 81406, 81407	G11.4, G82.2	33
	Hereditary Spastic Paraplegia Comrephensive Panel - Primary Genes (Invitae)	81448		
Congenital Myasthenic Syndrome				
Congenital Myasthenic Multigene Panel	Congenital Myasthenic Syndrome Panel (PreventionGenetics)	81406, 81407, , 81479	G70.2	21
	Congenital Myasthenic Syndrome Panel (Invitae)	81479		
Myotonia Congenita				
CLCN1 Sequencing and/or Deletion/Duplication Analysis	Myotonia Congenita via the *CLCN1* Gene (PreventionGenetics)	81406, 81479	G71.12	22
	CLCN1 Full Gene Sequencing and Deletion/Duplication (Invitae)			
Hypokalemic Periodic Paralysis				
CACNA1S and *SCN4A* Sequencing and/or Deletion/Duplication Analysis	*CACNA1S* Full Gene Sequencing and Deletion/Duplication (Invitae)	81479	E87.6, G72.3	23
	SCN4A Full Gene Sequencing and Deletion/Duplication (Invitae)	81406, 81479		
Other Covered Epilepsy, Neurodegenerative, and Neuromuscular Disorders				
Other Covered Epilepsy, Neuromuscular, and Neurodegenerative Disorders	See list below	81400-81408		27, 28, 29

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 (81161, 81404, 81405, 81406, 81407, 81408, 81479) 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 (for example: *SMN1, DMD, PMP22*) would be more appropriate, **OR**

      2. The member previously underwent single-gene analysis for a neuromuscular disorder (for example: *SMN1, DMD, PMP22*) and the results did not definitively lead to a diagnosis.

II. Comprehensive neuromuscular panel analysis to establish a genetic diagnosis for a neuromuscular disorder (81161, 81404, 81405, 81406, 81407, 81408, 81479) 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 (81185, 81186, 81189, 81403, 81404, 81405, 81406, 81407, 81408, 81460, 81465, 81479, 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 (81185, 81186, 81189, 81403, 81404, 81405, 81406, 81407, 81408, 81460, 81465, 81479, 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 and/or deletion/duplication analysis (81329, 81336, 81405, 0236U) 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 and/or deletion/duplication analysis (81329, 81336, 81405, 0236U) 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 (81329 is considered **medically necessary** when:

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

II. *SMN2* deletion/duplication analysis (81329) 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 (81401, 81403, 81404, 81405, 81406, 81407, 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 (81401, 81403, 81404, 81405, 81406, 81407, 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, 81479), *PSEN2* (81406), and/or *APP* (81406) sequencing and/or deletion/duplication analysis or multigene panel (81405, 81406, 81479) 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, 81479), *PSEN2* (81406), and/or *APP* (81406) sequencing and/or deletion/duplication analysis or multigene panel (81405, 81406, 81479) 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 81479) 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) (81179, 81403, 81404, 81405, 81406, 81407, 81479) 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) (81179, 81403, 81404, 81405, 81406, 81407, 81479) 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) 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) Elevated serum creatine kinase concentration, typically more than 10 times the normal levels, **OR**

b) For BMD, the member meets the following:

(1) The member has an elevated serum creatine kinase concentration, typically more than 5 times the normal levels, AND

(2) Any of the following:

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

(b) Activity-induced cramping

(c) Flexion contractures of the elbows

(d) Wheelchair dependency (after age 16 years)

(e) 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) 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)

FSHD1 Deletion/duplication or Haplotype Analysis, and/or *SMCHD1* and *DNMT3B* Sequencing and/or Deletion/duplication Analysis or Multigene Panel

I. *FSHD1* deletion/duplication or haplotype analysis (81404), and/or *SMCHD1* (81479) and *DNMT3B* sequencing and/or deletion/duplication analysis (81479) or multigene panel analysis (81404) 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. *FSHD1* deletion/duplication or haplotype analysis (81404), and/or *SMCHD1* (81479) and *DNMT3B* sequencing and/or deletion/duplication analysis (81479) or multigene panel analysis (81404) 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) or sequencing analysis (81286) to establish or confirm a diagnosis of Friedreich's Ataxia is considered **medically necessary** when:

A. The member has at least two of the following from 1-6:

1. Neurologic findings, typically with onset before age 25 years
    a) Progressive ataxia of gait and limbs
    b) Dysarthria
    c) Decrease in/loss of position sense and/or vibration sense in lower limbs
    d) Pyramidal weakness of the legs, extensor plantar responses, **AND/OR**
2. Musculoskeletal features:
    a) Muscle weakness
    b) Scoliosis
    c) Pes cavus, **AND/OR**

3. Hypertrophic non-obstructive cardiomyopathy, **AND/OR**
4. Endocrinologic features:
    a) Glucose intolerance
    b) Diabetes mellitus, **AND/OR**
5. Optic atrophy and/or deafness, **AND/OR**
6. Family history consistent with autosomal recessive inheritance, **AND**
7. Non-genetic causes for the ataxia have been ruled out (examples: alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, tumors)

II. *FXN* repeat analysis (81284) and sequencing analysis (81286) 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) is considered **medically necessary** when:

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

1. Progressive motor disability featuring chorea, where voluntary movement may also be affected, **OR**
2. Cognitive decline, **OR**
3. Changes in personality, **OR**
4. Depression, **OR**

5. Family history of any of the above symptoms consistent with autosomal dominant inheritance, **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) 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 (EXAMPLES: 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 (81324, 81325, 81403, 81404, 81405, 81406, 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, **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**

1. Has a close relative diagnosed with an inherited peripheral neuropathy, **AND**

C. 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 (81324, 81325, 81403, 81404, 81405, 81406, 81479) to establish a genetic diagnosis of an inherited peripheral neuropathy 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 (81161, 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 (81161, 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) and/or *CNBP* repeat analysis (81187) 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) and *CNBP* repeat analysis (81187) 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 (81404, 81405, 81406, 81407, 81408, 81479) 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 (81404, 81405, 81406, 81407, 81408, 81479) 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* (81408, 81479), *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* (81408, 81479), *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 (81404, 81405, 81406, 81407, 81448) 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, **AND**

B. A multigene panel must include the following genes, at a minimum: *SPAST, ATL1, KIF1A, CYP7B1, SPG7, SPG11*.

II. Multigene panel analysis to establish a genetic diagnosis of hereditary spastic paraplegia (81404, 81405, 81406, 81407, 81448) 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 (81406, 81407, 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 (81406, 81407, 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, 81479) 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 (less than or equal to 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, 81479) 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 less than 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 less than 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 one or more 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

Comprehensive Neuromuscular Disorders Panel

American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM)

The American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) developed a position statement in 2016 regarding the clinical usefulness of genetic testing in the diagnosis of neuromuscular disease. “The AANEM believes that genetic testing and arriving at a specific molecular diagnosis is critical to providing high quality care to NM [neuromuscular] patients.” (page 1007) The same statement also remarks: “There is a role for single gene testing in cases with characteristic phenotypes, in addition to larger gene panels…” (page 1007)

Winder et al (2020)

Winder et al published a study in 2020 in Neurology: Genetics which reported results of genetic testing of 25,356 individuals who were suspected to have a neuromuscular disorder. Twenty percent of the cohort was found to have a definitive molecular diagnosis. (page 3) The authors comment: “Multigene NGS [next generation sequencing] analysis advances the interpretation of heterogeneity for any single clinical disorder and also helps refine differential diagnoses. Panels can also be useful for individuals for whom a

single-gene test cannot be confidently selected because of a mild or uncharacteristic phenotype." (page 7) Regarding the utility of a larger, multi-gene panel, the authors also note that "...in 2,501 instances in which a clinician received a negative result for a single-gene or small panel test and subsequently pursued testing using a larger panel, a positive diagnostic result was obtained for 200 individuals." (page 7)

Comprehensive Ataxia Panel

American College of Medical Genetics and Genomics (ACMG)

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."

SCN1A Seizure Disorders and Epilepsy Multigene Panels

Berg AT, Berkovic SF, Brodie MJ, et al 2010
This report from the International League Against Epilepsy (ILAE) Commission on Classification and Terminology stated the following:

"Conceptually, there is a distinct other structural or metabolic condition or disease that has been demonstrated to be associated with a substantially increased risk of developing epilepsy in appropriately designed studies. Structural lesions of course include acquired disorders such as stroke, trauma, and infection. They may also be of genetic origin (e.g.,

tuberous sclerosis, many malformations of cortical development); however, as we currently understand it, there is a separate disorder interposed between the genetic defect and the epilepsy."

GeneReviews

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The recommendations for genetic testing for epilepsy (especially *SCN1A*) are as follows:

"*SCN1A* seizure disorders encompass a spectrum that ranges from simple febrile seizures and generalized epilepsy with febrile seizures plus (GEFS+) at the mild end to Dravet syndrome and intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC) at the severe end."

"*SCN1A* seizure disorders encompass a spectrum of phenotypes that ranges from mild to severe. When the following suggestive features are present, *SCN1A* molecular genetic testing should be considered:

• Precipitation of seizure with fever, warmth, or vaccination

• Prolonged or hemiconvulsive seizures

• Seizure provocation with overstimulation or flashing/patterned visual stimulus

• Worsening of seizures with medications that inhibit sodium channel function as the primary mechanism of action (e.g., carbamazepine, oxcarbazepine, phenytoin, lamotrigine)."

"Because the phenotype of *SCN1A* seizure disorders is indistinguishable from many other inherited disorders with seizures, the recommended molecular genetic testing is an epilepsy multigene panel."

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

American College of Medical Genetics and Genomics (ACMG) and National Society of Genetic Counselors (NSGC)

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*).

APOE, TREM2, and Other Variant Analysis

American Academy of Neurology

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 College of Medical Genetics and Genomics (ACMG)

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.”

DMD Sequencing and/or Deletion/Duplication Analysis

American Academy of Pediatrics

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

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."

FSHD1 Deletion/Duplication or Haplotype Analysis and/or SMCHD1 and DNMT3B Sequencing and/or Deletion Analysis or Multigene Panel

American Academy of Neurology and American Association of Neuromuscular & Electrodiagnostic Medicine

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.

Huntington Disease

GeneReviews

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The recommended testing for Huntington Disease is as follows:

Huntington disease (HD) should be suspected in individuals with any of the following:

- Progressive motor disability featuring chorea. Voluntary movement may also be affected.
- Mental disturbances including cognitive decline, changes in personality, and/or depression
- Family history consistent with autosomal dominant inheritance

Predictive Testing for Huntington Disease

The risk to the sibs of a proband depends on the genetic status of the proband's parents:

- If a parent has an *HTT* allele with CAG length of 40 or greater, the risk to the sibs of inheriting a full-penetrance HD-causing allele is 50%.
- If a parent has an *HTT* allele with reduced penetrance (36-39 CAG repeats), the risk to the sibs of inheriting a pathogenic HD-causing allele (of either reduced or full penetrance) is 50%.
- If a parent has an intermediate *HTT* allele (27-35 CAG repeats), the risk to the sibs of inheriting a CAG expansion greater than 35 repeats or a "new HD-causing allele" depends on a variety of factors, including the following:

- **The CAG size of the allele.** Larger CAG sizes are more prone to expansion. CAG size-specific estimates for repeat instability in sperm have been reported to enable genetic counselors to provide more accurate risk assessment for persons who receive an intermediate allele predictive test result. While all intermediate CAG repeat sizes were shown to have the possibility of expansion, the probability of expansion increases dramatically with increasing CAG size; approximately 21% of 35 CAG alleles expanded into the disease-associated range. Evidence-based genetic counseling implications for intermediate allele predictive test results have been published.
- **The sex and age of the transmitting parent.** Paternally inherited intermediate alleles are more prone to CAG expansion than maternally inherited intermediate alleles; maternal expansions are extremely rare. Expanded intermediate alleles are preferentially transmitted by males with advanced paternal age.
- **The DNA sequence in *cis* configuration with the CAG expansion.** CAG tracts interrupted with CAA and CCG trinucleotides are more stable.

Offspring of a proband

- At conception, each child of an individual with HD as a result of heterozygosity for a CAG repeat expansion in *HTT* has a 50% chance of inheriting the HD-causing allele. Offspring who inherit a:
  - **Reduced-penetrance allele (36-39 CAG repeats)** are at risk for HD but may not develop symptoms
  - **Full-penetrance allele (40 or more CAG repeats)** are at risk of developing HD with increased certainty assuming a normal life span.
- Each child of an affected individual who is homozygous for CAG repeat expansion in *HTT* will inherit an HD-causing allele.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected or has a CAG expansion in *HTT*, his or her family members are at risk.

PMP22 Sequencing and/or Deletion/Duplication Analysis or Multigene Panel

GeneReviews

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

The most common type of Charcot-Marie Tooth (CMT) (Type 1a) is caused by a duplication of *PMP22*. The clinical findings for Charcot-Marie-Tooth hereditary neuropathy (Bird, updated 2022) in the Clinical Characteristics of Charcot-Marie Tooth Hereditary Neuropathy section are as follows:

> The affected individual typically has distal muscle weakness and atrophy, weak ankle dorsiflexion, depressed tendon reflexes, and pes cavus foot deformity (i.e., high-arched feet).
>
> Muscle weakness is often associated with mild to moderate distal sensory loss.

Additionally, Bird (updated 2022) lists the following genes as the most commonly involved genes in CMT: *GDAP1, GJB1, HINT1, MFN2, MPZ, PMP22, SH3TC2, SORD* (Table 4).

Hereditary neuropathy with liability to pressure palsies (HNPP) is caused by a deletion or sequence variants in *PMP22*. Typical clinical findings for HNPP according to Crestian (updated 2020, in the Suggestive Findings section) are as follows:

- Recurrent acute focal sensory and motor neuropathies mainly at entrapment sites
- Painless nerve palsy after minor trauma or compression
- Evidence on physical examination of previous nerve palsy such as focal weakness, atrophy, or sensory loss
- Complete spontaneous recovery from neuropathies (in 50% of occurrences) within weeks
- Mild-to-moderate pes cavus foot deformity (in 4%-40% of individuals)

Additionally, in the evaluation of relatives at risk, the following is recommended (Crestian, updated 2020):

> Asymptomatic relatives at risk may wish to clarify their genetic status by undergoing molecular genetic testing for the *PMP22* pathogenic variant identified in an affected family member in order to be advised about agents and circumstances to avoid.

LGMD Multigene Panel

American Academy of Neurology and American Association of Neuromuscular and Electrodiagnostic Medicine

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)."

DMPK and/or CNBP Repeat Analysis

Myotonic Dystrophy Foundation

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."

Fifteen 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."

Hereditary Dystonia Multigene Panel

GeneReviews

Per GeneReviews "Hereditary Dystonia Overview" (last update: June 22, 2017), dystonia is defined as "a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements and/or postures. Dystonic movements are typically patterned and twisting, and may be associated with tremor. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation. Most forms of dystonia tend to worsen initially." Multiple genes have been implicated in hereditary dystonia, representing a variety of inheritance patterns such as autosomal dominant, autosomal recessive, mitochondrial, and X-linked inheritance.

Spastic Paraplegia Multigene Panel

GeneReviews: Hereditary Spastic Paraplegia Overview

On neurological examination, individuals with hereditary spastic paraplegia have the following:

- Bilateral lower-extremity spasticity (maximal in hamstrings, quadriceps, adductors, and gastrocnemius-soleus muscles) and weakness (maximal in the iliopsoas,

hamstring, and tibialis anterior muscles). Spasticity and weakness are variable. Some individuals have spasticity and no demonstrable weakness, whereas others have spasticity and weakness in approximately the same proportions.
- Lower-extremity hyperreflexia and extensor plantar responses
- Often, mildly impaired vibration sensation in the distal lower extremities

Tables 1 and 2 list genes associated with hereditary spastic paraplegia, of both autosomal dominant and autosomal recessive inheritance.

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