BlueCross BlueShield Nebraska

GENETIC TESTING: EPILEPSY, NEURODEGENERATIVE AND NEUROMUSCULAR DISORDERS (PREAUTHORIZATION REQUIRED)

V.65

V.65 GENETIC TESTING: EPILEPSY, NEURODEGENERATIVE AND NEUROMUSCULAR DISORDERS (PREAUTHORIZATION REQUIRED)

DESCRIPTION

Genetic testing for hereditary epilepsy, neurodegenerative, and neuromuscular conditions may be used to establish or confirm a diagnosis in a patient who has signs and/or symptoms of genetic disorder, for whom clinical evaluation and other standard laboratory tests/imaging etc have been non-diagnostic or inconclusive. Confirming a genetic diagnosis may inform clinical management or eliminate the need for further diagnostic workup. This document addresses genetic testing for epilepsy, neurodegenerative and neuromuscular genetic diseases.

Dates

Original Effective
03-01-2021
Last Review
08-07-2024
Next Review
08-11-2025

RELATED POLICIES

- ***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.

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.

REFERENCE TABLE

The tests, associated laboratories, CPT codes, and ICD codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Platform for a comprehensive list of registered tests.

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Re
Comprehensive Neuromuscular Disorders Panel				
Comprehensive Neuromuscular Disorders Panel	Comprehensive Neuromuscular Panel (PreventionGenetics, part of Exact Sciences)	81161, 81404, 81405, 81406, 81479	G12, G13, G23-G26, G31, G32, G36, G37	22, 27, 31,
	Comprehensive Neuromuscular Disorders Panel (Invitae)			
	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	12
	Genomic Unity Comprehensive Ataxia Analysis (Variantyx, Inc.)	0217U		

Spinal Muscular Atrophy				
SMN1 Sequencing and/or Deletion/Duplication Analysis	Spinal Muscular Atrophy (SMA), Diagnostic (Quest Diagnostics)	81329	G12, Z84.81	7
	SMN1 Sequencing Analysis (Fulgent Genetics)	81336, 81405		
	Genomic Unity SMN1/2 Analysis (Variantyx Inc.)	0236U		
SMN2 Deletion/Duplication Analysis	SMN2 Deletion/Duplication (GeneDx)	81401		
Rett Syndrome				
MECP2 Sequencing and/or Deletion/Duplication Analysis	MECP2 Full Gene Sequencing and Deletion/Duplication (Invitae)	81302, 81304	F70-F79, F80, F81, F82, F84, F88, F89, Z13.4, Z82.79, Z84	36
	MECP2 Gene Sequencing & Del/Dup (GeneDx)			
	Genomic Unity MECP2 Analysis (Variantyx, Inc.)	0234U		
Epilepsy				
Epilepsy Multigene Panel	Comprehensive Epilepsy Panel (Blueprint Genetics)	81185, 81189, 81302, 81406, 81419, 81479	G40.001-G40.919	32
	Comprehensive Epilepsy Panel (GeneDx)			
	Clinical Epilepsy NGS Panel (LabCorp)			
	EpilepsyNext (Ambry Genetics)			
	Epilepsy Panel (Invitae)			
CADASIL				
NOTCH3 Sequencing and/or Deletion/Duplication Analysis	NOTCH3 Full Gene Sequencing and Deletion/Duplication (Invitae)	81406, 81479	I67.850, F02.80, F02.81	37
Alzheimer Disease				
PSEN1, *PSEN2*, and *APP* Sequencing and/or Deletion/Duplication Analysis	PSEN1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81405, 81479	F03, G30, G31.1, R41.0, R41.81, Z13.858,	4, 5
	Alzheimer's Disease, Familial via the PSEN2 Gene (PreventionGenetics, part of Exact Sciences)	81406, 81479		

	(PreventionGenetics, part of Exact Sciences)	81479		
	Hereditary Alzheimer's Disease Panel (Invitae)			
APOE Variant Analysis for Alzheimer's Disease	APOE Single Gene Test (Blueprint Genetics)	81401, 81479, S3852		2
Amyotrophic Lateral Sclerosis (ALS)				
Amyotrophic Lateral Sclerosis (ALS) Multigene Panel	Amyotrophic Lateral Sclerosis (ALS) Panel (PreventionGenetics, part of Exact Sciences)	81179, 81403, 81404, 81405, 81406, 81407, 81479, S3800	G12.21	10,
	Amyotrophic Lateral Sclerosis Panel (Invitae)			
Duchenne and Becker Muscular Dystrophy				
Diagnostic *DMD* Sequencing and/or Deletion/Duplication Analysis	Dystrophinopathies Test (Invitae)	81161	G71.01, R62.59, Z84.81	11,
	Duchenne/Becker MD (DMD) Gene Sequencing (GeneDx)	81408		
	Genomic Unity DMD Gene Analysis (Variantyx)	0218U		
Facioscapulohumeral Muscular Dystrophy (FSHD)				
D4Z4 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, 2
	Facioscapulohumeral Muscular Dystrophy 2 via the SMCHD1 Gene (PreventionGenetics, part of Exact Sciences)	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, 81479		
Friedreich's Ataxia				
FXN Repeat Analysis and/or Sequencing Analysis	Friedreich Ataxia (FXN) Repeat Expansion Test (Athena Diagnostics)	81284, 81285	G11, Z84.81	9, 1

	Genomic Unity FXN Analysis (Variantyx Inc)	0233U		
Huntington's Disease (HD)				
HTT Repeat Analysis	Huntington Disease (HTT) Genetic Testing (Repeat Expansion) (LabCorp)	81271, 81274	G10, Z84.81	8, 1 38
Inherited Peripheral Neuropathy (Charcot-Marie-Tooth and Hereditary Neuropathy with Liability to Pressure Palsies)				
PMP22 Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	Deletion/Duplication (PMP22) (GeneDx)	81324	G60.0, G60.8, G60.9	3, 1
	PMP22 DNA Sequencing Test (Quest Diagnostics)	81325		
	Charcot-Marie Tooth (CMT) - Comprehensive Panel (PreventionGenetics, part of Exact Sciences)	81448		
	Charcot-Marie-Tooth Disease NGS Panel (HNL Lab Medicine)			
Limb-Girdle Muscular Dystrophies (LGMD)				
Limb Girdle Muscular Dystrophy Multigene Panel	Limb-Girdle Muscular Dystrophy Panel (GeneDx)	81405, 81406, 81408, 81479	G71.0, Z13.71, Z82.0, Z84.81	6, 4
	Limb-Girdle Muscular Dystrophy Panel (Invitae)			
Myotonic Dystrophy				
DMPK and/or *CNBP* (ZNF9) Repeat Analysis	Myotonic Dystrophy 1 (DMPK) Genetic Testing (Repeat Expansion) (LabCorp)	81234, 81239, 81401, 81404, S3853	G71.11, Z84.81	15, 16, 17, 18,
	Myotonic Dystrophy 2 (ZNF9 / CNBP) Genetic Testing (Repeat Expansion) (LabCorp)	81187, S3853		
Hereditary Dystonia				
Hereditary Dystonia Multigene Panel	Dystonia Panel (GeneDx)	81404, 81405, 81406, 81407, 81408, 81479	G24.1, G24.9	19
	Dystonia Panel (PreventionGenetics, part of Exact Sciences)			
	Dystonia Comprehensive Panel (Invitae)			
Parkinson Disease				

	Invitae Parkinson Disease and Parkinsonism Panel (Invitae)			
Hereditary Spastic Paraplegia				
Hereditary Spastic Paraplegia Multigene Panel	Spastic Paraplegia Panel (Blueprint Genetics) Hereditary Spastic Paraplegia Comprehensive Panel (Invitae)	81448	G11.4, G82.2	21
Congenital Myasthenic Syndrome				
Congenital Myasthenic Syndromes Multigene Panel	Congenital Myasthenic Syndrome Panel (PreventionGenetics, part of Exact Sciences) Congenital Myasthenic Syndrome Panel (Invitae)	81406, 81407, 81479	G70.2	22
Myotonia Congenita				
CLCN1 Sequencing and/or Deletion/Duplication Analysis	Myotonia Congenita via the *CLCN1* Gene (PreventionGenetics, part of Exact Sciences) CLCN1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81406, 81479	G71.12	23,
Hypokalemic Periodic Paralysis				
CACNA1S and *SCN4A* Sequencing and/or Deletion/Duplication Analysis, or Periodic Paralysis Multigene Panel	*CACNA1S* Full Gene Sequencing and/or Deletion/Duplication (Invitae) *SCN4A* Full Gene Sequencing and/or Deletion/Duplication (Invitae)	81406, 81479	E87.6, G72.3	24
Other Covered Epilepsy, Neurodegenerative, and Neuromuscular Disorders				
Other Covered Epilepsy, Neuromuscular, and Neurodegenerative Disorders	See list below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479		28, 29,

POLICY

COMPREHENSIVE NEUROMUSCULAR DISORDERS PANEL

A. The member meets either of the following:

1. The member is a neonate and displays at least one of the following:

    a) Respiratory insufficiency, with sudden episodic apnea and cyanosis, **OR**

    b) Joint contractures (e.g., arthrogryposis multiplex congenita), **OR**

    c) Stridor, **OR**

    d) Feeding difficulties, **OR**

    e) Poor suck/cry, **OR**

    f) Choking spells, **OR**

    g) Facial, bulbar, or generalized weakness, **OR**

2. The member is any age and displays at least one of the following:

    a) Abnormal muscle fatigability/weakness, **OR**

    b) Delayed motor milestones, **OR**

    c) Eyelid ptosis or extraocular muscle weakness, **OR**

    d) Facial and bulbar weakness with nasal speech and difficulties in coughing and swallowing, **OR**

    e) Spinal deformity or muscle atrophy, **OR**

    f) Abnormal electromyography (EMG) testing showing a defect in neuromuscular transmission, **OR**

    g) Elevated serum creatine kinase levels, **AND**

B. The member meets one of the following:

1. The member's presentation is not consistent with a neuromuscular disorder for which targeted or single-gene analysis (e.g., *SMN1, DMD, PMP22*) is appropriate, **OR**
2. The member underwent targeted or single-gene analysis for a neuromuscular disorder (e.g., *SMN1, DMD, PMP22*) and the results were non-diagnostic.

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COMPREHENSIVE ATAXIA PANEL

I. Comprehensive ataxia panel analysis to establish a genetic diagnosis of an ataxia (0216U, 0217U, 81185, 81189, 81286, 81403, 81404, 81479) is considered **medically necessary** when:
   A. The member displays one or more of the following:
      1. Poorly coordinated gait and finger/hand movements, **OR**
      2. Weakness of the eye muscles (ophthalmoplegia), **OR**
      3. Dysarthria, **OR**
      4. 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 (0216U, 0217U, 81185, 81189, 81286, 81403, 81404, 81479) is considered **investigational** for all other indications.

SPINAL MUSCULAR ATROPHY

***SMN1* Sequencing and/or Deletion/Duplication Analysis**

I. *SMN1* sequencing and/or deletion/duplication analysis (0236U, 81329, 81336 81405) to establish or confirm a diagnosis of spinal muscular atrophy (SMA) is considered **medically necessary** when:
   A. The member has a positive newborn screen for SMA, **OR**
   B. The member has any of the following:
      1. History of motor difficulties, especially with loss of skills, **OR**
      2. Muscle weakness, especially proximal muscles, **OR**
      3. Hypotonia, **OR**
      4. Areflexia/hyporeflexia, **OR**
      5. Tongue fasciculations, **OR**
      6. Hand tremor, **OR**
      7. Recurrent lower respiratory tract infections or severe bronchiolitis in the first few months of life, **OR**
      8. Evidence of motor unit disease on electromyogram.

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

***SMN2* Deletion/Duplication Analysis**

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

RETT SYNDROME

***MECP2* Sequencing and/or Deletion/Duplication Analysis**

I. *MECP2* sequencing and/or deletion/duplication analysis (0234U, 81302, 81304) to establish or confirm a diagnosis of Rett syndrome is considered **medically necessary** when:

A. The member experienced a period of developmental regression (range: ages 1-4 years) followed by recovery or stabilization (range: ages 2-10 years), **AND**

B. The member has at least one of the following:

1. Partial or complete loss of acquired purposeful hand skills, **OR**
2. Partial or complete loss of acquired spoken language or language skill (e.g., babble), **OR**
3. Gait abnormalities: impaired (dyspraxic) or absence of ability, **OR**
4. Stereotypic hand movements including hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms, **AND**

C. The member does **not** have either of the following:

1. Brain injury secondary to peri- or postnatal trauma, neurometabolic disease, or severe infection that causes neurological problems, **OR**
2. Grossly abnormal psychomotor development in the first six months of life, with early milestones not being met.

II. *MECP2* sequencing and/or deletion/duplication analysis (0234U, 81302, 81304) to establish or confirm a diagnosis of Rett syndrome is considered **investigational** for all other indications.

EPILEPSY

Epilepsy Multigene Panel

I. The use of an epilepsy multigene panel (81185, 81189, 81302, 81406, 81419, 81479) is considered **medically necessary** when:

A. The member has a history of unexplained epilepsy (i.e., seizures not caused by acquired etiology such as trauma, infection,

CADASIL

***NOTCH3* Sequencing and/or Deletion/Duplication Analysis**

I. *NOTCH3* sequencing and/or deletion/duplication analysis (81406, 81479) to establish or confirm a diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is considered **medically necessary** when:

A. The member has a family history of stroke and/or vascular dementia consistent with an autosomal dominant pattern of inheritance, **OR**

B. The member has at least one of the following clinical features of CADASIL:

1. Transient ischemic attacks and ischemic stroke, **OR**
2. Cognitive impairment, manifesting initially with executive dysfunction, with a concurrent stepwise deterioration due to recurrent strokes to vascular dementia, **OR**
3. Migraine with aura (mean age of onset of 30 years), **OR**
4. Psychiatric disturbances, most frequently mood disturbances and apathy, **OR**

C. The member has at least one of the following brain imaging findings of CADASIL:

1. Symmetric and progressive white matter hyperintensities, often involving the anterior temporal lobes and external capsules, **OR**
2. Lacunes of presumed vascular origin, **OR**
3. Recent subcortical infarcts, **OR**
4. Dilated perivascular spaces, sometimes referred to as subcortical lacunar lesions, **OR**
5. Brain atrophy, **OR**
6. Cerebral microbleeds.

II. *NOTCH3* sequencing and/or deletion/duplication analysis (81406, 81479) to establish or confirm a diagnosis of

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ALZHEIMER DISEASE

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

I. *PSEN1* (81405, 81479), *PSEN2* (81406, 81479), and/or *APP* (81406, 81479) sequencing and/or deletion/duplication analysis to establish a diagnosis or determine future risk to develop early-onset Alzheimer disease (diagnosed before age 65 years) is considered **medically necessary** when:

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

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

1. Has a family history of dementia that is consistent with an autosomal dominant pattern of inheritance, **AND**

a) Has at least one relative with a history of early-onset Alzheimer disease (diagnosed before age 65 years), **OR**

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

1. Was diagnosed with dementia at 65 years of age or younger, **AND**

a) Has a close relative diagnosed with dementia, **OR**

b) Has an unknown family history (e.g., adoption), **OR**

2. Was diagnosed with dementia at 66 years of age or older, **AND**

a) Has a family history of dementia that is consistent with an autosomal dominant pattern of inheritance, **AND**

b) Has at least one close relative who was diagnosed with dementia at 65 years of age or younger.

II. Genetic testing for Alzheimer's disease via other genes is considered **investigational.****

III. *PSEN1* (81405, 81479), *PSEN2* (81406, 81479), and/or *APP* (81406, 81479) sequencing and/or deletion/duplication analysis to establish the diagnosis or determine future risk to develop early-onset Alzheimer disease (diagnosed before age 65 years) is considered **investigational** for all other indications.

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NOTE: Please see clinical guidelines "*APOE* Variant Analysis for Alzheimer's Disease" for coverage criteria for *APOE* testing

APOE Variant Analysis for Alzheimer's Disease

I. *APOE* variant analysis (81401, 81479, S3852) is considered **medically necessary** when:
   A. The member has a diagnosis of Alzheimer's disease, **AND**
   B. The member is being evaluated for suitability of treatment with monoclonal antibodies directed against aggregated forms of beta amyloid (such as Leqembi or Kisunla).

II. *APOE* variant analysis (81401, 81479, S3852) is considered **investigational** for all other indications

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic Lateral Sclerosis (ALS) Multigene Panel

I. Multigene panel analysis to establish a genetic etiology of amyotrophic lateral sclerosis (ALS) (81179, 81403, 81404, 81405, 81406, 81407, 81479, S3800) is considered **medically necessary** when:
   A. The member displays all of the following:
      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**
   B. 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, S3800) is considered **investigational** for all other indications.

DUCHENNE AND BECKER MUSCULAR DYSTROPHY

Diagnostic _DMD_ Sequencing and/or Deletion/Duplication Analysis

I. *DMD* sequencing and/or deletion/duplication analysis (0218U, 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 has all of the following clinical characteristics of DMD:
      1. Progressive symmetric muscular weakness - proximal greater than distal, often with calf hypertrophy (enlargement), **AND**
      2. Symptoms presenting before age five years, **AND**
      3. Wheelchair dependency before age 13 years, **AND**

1. Elevated serum creatine kinase concentration, typically more than 5 times the normal levels, **AND**

a) At least one of the following:

(1) Progressive symmetric muscle weakness (proximal more so than distal) often with calf hypertrophy (weakness of quadriceps femoris in some cases the only sign), **OR**

(2) Activity-induced cramping, **OR**

(3) Flexion contractures of the elbows, **OR**

(4) Wheelchair dependency after age 16 years, **OR**

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

C. The member is asymptomatic (male or female), **AND**
1. Has a biological sibling with a clinical diagnosis of Duchenne or Becker muscular dystrophy, **OR**
2. Has a biological mother that is an obligate carrier for Duchenne or Becker muscular dystrophy, **OR**

D. The member is an asymptomatic female, **AND**
1. Has a first- or second-degree relative with a clinical diagnosis of Duchenne or Becker muscular dystrophy.

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

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

D4Z4 Haplotype Analysis, and/or *SMCHD1* and *DNMT3B* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel

I. D4Z4 haplotype analysis (81404), and/or *SMCHD1* (81479) and *DNMT3B* (81479) sequencing and/or deletion/duplication analysis 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:

or bulbar muscle weakness, **OR**

2. Progression of weakness after pregnancy, **OR**

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

II. D4Z4 haplotype analysis (81404), and/or *SMCHD1* (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.

FRIEDREICH'S ATAXIA

***FXN* Repeat Analysis and/or Sequencing Analysis**

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

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

1. The member has at least two of the following:

a) Progressive ataxia of the gait and limbs (e.g., cerebellar ataxia), **OR**

b) Dysarthria, **OR**

c) Decrease in/loss of position sense and/or vibration sense in lower limbs, **OR**

d) Pyramidal weakness of the legs, **OR**

e) Extensor plantar responses/Babinski signs, **OR**

f) Muscle weakness, **OR**

g) Scoliosis, **OR**

h) Pes cavus (flat feet), **OR**

i) Hypertrophic nonobstructive cardiomyopathy, **OR**

j) Glucose intolerance or diabetes mellitus, **OR**

k) Optic atrophy and/or deafness, **AND**

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

1. Has a biological sibling with Friedreich's ataxia.

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

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

HUNTINGTON'S DISEASE

***HTT* Repeat Analysis**

I. *HTT* repeat analysis to establish a diagnosis or for predictive testing of Huntington's disease (HD) (81271, 81274) is considered **medically necessary** when:
   A. The member displays clinical features of Huntington's disease (i.e, progressive motor disability featuring chorea, where voluntary movement may also be affected), **OR**
   B. The member has a clinical diagnosis of Huntington's disease, **OR**
   C. The member is undergoing predictive testing*, **AND**
      1. The member is presymptomatic/asymptomatic, **AND**
      2. The member is 18 years of age or older**, 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. *HTT* repeat analysis to establish a diagnosis or for predictive testing of Huntington's disease (HD) (81271, 81274) is considered **investigational** for all other indications.

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

INHERITED PERIPHERAL NEUROPATHIES (EXAMPLES: CHARCOT-MARIE-TOOTH DISEASE AND HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES)

I. *PMP22* sequencing and/or deletion/duplication analysis (81324, 81325) or multigene panel analysis (81448) to establish a genetic diagnosis of an inherited peripheral neuropathy is considered **medically necessary** when:
   A. The member displays one or more of the following:
      1. Distal muscle weakness and atrophy, **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. Evidence on physical examination of previous nerve palsy such as focal weakness, atrophy, or sensory loss, **OR**
      8. Complete spontaneous recovery from neuropathies.

II. *PMP22* sequencing and/or deletion/duplication analysis (81324, 81325) or multigene panel analysis (81448) to establish a genetic diagnosis of an inherited peripheral neuropathy is considered **investigational** for all other indications.

LIMB-GIRDLE MUSCULAR DYSTROPHY (LGMD)

Limb-girdle Muscular Dystrophy Multigene Panel

I. Multigene panel analysis to establish a diagnosis of limb-girdle muscular dystrophy (81405, 81406, 81408, 81479) is considered **medically necessary** when:
   A. The member displays slowly progressive, symmetrical weakness, **AND**
   B. The member has any of the following features:
      1. Limb-girdle pattern of weakness affecting proximal muscles of the arms and legs, **OR**
      2. Scapuloperoneal weakness, **OR**
      3. Distal weakness, **OR**
      4. Elevated serum creatine kinase levels, **OR**
   C. The member is asymptomatic, **AND**
      1. The member 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 (81405, 81406, 81408, 81479) is considered **investigational** for all other indications.

MYOTONIC DYSTROPHY

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

A. The member meets either of the following:
1. The member is a neonate with two or more of the following:
a) Hypotonia, **OR**
b) Facial muscle weakness, **OR**
c) Generalized weakness, **OR**
d) Positional malformations, including clubfoot, **OR**
e) Respiratory insufficiency, **OR**
2. The member is any age and displays any one of the following:
a) Muscle weakness, especially of the distal leg, hand, neck, and face, **OR**
b) Myotonia, which often manifests as the inability to quickly release a hand grip (grip myotonia), **OR**
c) Posterior subcapsular cataracts, **OR**
d) Cardiac conduction defects or progressive cardiomyopathy, **OR**
e) Insulin insensitivity, **OR**
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.

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

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 a clinical presentation consistent with dystonia or patterns of abnormal, repetitive, dystonic movements.

BlueCross BlueShield Nebraska

PARKINSON DISEASE

Parkinson Disease Multigene Panel

I. Multigene panel testing (81479) to establish a genetic diagnosis of Parkinson disease is considered **medically necessary** when:
   A. The member has a clinical diagnosis of Parkinson disease, **AND**
   B. The member has a family history of Parkinson disease.

II. Multigene panel testing (81479) to establish a genetic diagnosis of Parkinson disease is considered **investigational** for all other indications.

HEREDITARY SPASTIC PARAPLEGIA

Hereditary Spastic Paraplegia Multigene Panel

I. Multigene panel analysis to establish a genetic diagnosis of hereditary spastic paraplegia (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.

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

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 any of the following:
      1. Neonatal respiratory insufficiency, with sudden episodic apnea and cyanosis, **OR**
      2. Neonatal joint contractures (e.g., arthrogryposis multiplex congenita), **OR**
      3. Stridor, feeding difficulties, poor suck/cry, choking spells, eyelid ptosis, and/or facial, bulbar, or generalized weakness in

6. Eyelid ptosis or extraocular muscle weakness, **OR**
7. Facial and bulbar weakness with nasal speech and difficulties in coughing and swallowing, **OR**
8. Spinal deformity or muscle atrophy, **OR**
9. Abnormal electromyography (EMG) testing showing a defect in neuromuscular transmission.

II. Multigene panel analysis to establish a genetic diagnosis of congenital myasthenic syndromes (81406, 81407, 81479) is considered **investigational** for all other indications.

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 any of the following:
      1. Episodes of muscle stiffness (myotonia) or cramps beginning in early childhood that are alleviated by brief exercise, **OR**
      2. Myotonic contraction is elicited by percussion of muscles, **OR**
      3. 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.

HYPOKALEMIC PERIODIC PARALYSIS

***CACNA1S* and *SCN4A* Sequencing and/or Deletion/Duplication Analysis, or Periodic Paralysis Multigene Panel**

I. *CACNA1S* and *SCN4A* sequencing and/or deletion/duplication analysis, or Periodic Paralysis Multigene Panel (81406, 81479) to establish a genetic diagnosis of periodic paralysis is considered **medically necessary** when:
   A. Alternative causes of hypokalemia have been excluded (e.g., renal, adrenal, thyroid dysfunction; renal tubular acidosis; diuretic and laxative abuse), **AND**
   B. The member has had two or more attacks of muscle weakness with documented serum potassium less than 3.5 mEq/L, **OR**
   C. The member has had one attack of muscle weakness, **AND**
      1. Has a close relative who has had one attack of muscle weakness with documented serum potassium less than 3.5 mEq/L, **OR**

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.

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

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. AADC deficiency
   B. Hereditary Transthyretin Amyloidosis
   C. X-linked Adrenoleukodystrophy
   D. L1 Syndrome
   E. SCN9A Neuropathic Pain Syndromes
   F. Cerebral Cavernous Malformation, Familial
   G. 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 and Molecular Testing* (see policy for coverage criteria).

NOTE: 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.

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

uncles, great grandchildren, and first cousins

2. **Early-onset Alzheimer disease** is defined as Alzheimer disease occurring in an individual under age 65
3. A **neonate** is a baby who is four weeks old or younger
4. **Childhood** is the period of development until the 18th birthday.
5. **Myotonia** is defined as impaired relaxation of skeletal muscle after voluntary contraction.
6. **Autosomal dominant** inheritance patterns are generally characterized by the following traits:
   a. There are individuals with the condition in multiple generations of a family
   b. Individuals who do not have the condition do not have children with the condition
   c. Individuals with the condition have a parent with the condition

NOTE: Factors such as incomplete penetrance (when not all individuals with a genetic variant develop symptoms) and variable expressivity (when symptoms/signs or severity of the condition vary from person to person) can complicate the identification of this pattern of inheritance.

BACKGROUND

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.” The same statement also remarks: “There is a role for single gene testing in cases with characteristic phenotypes, in addition to larger gene panels…”. (p. 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. (p. 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

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." (p. 7)

Nicolau et al (2021)

In 2021, recommendations for genetic testing of muscle and neuromuscular junction disorders were proposed by Nicolau et al (peer reviewed by *American Association of Neuromuscular & Electrodiagnostic Medicine (*AANEM). They state that the overall approach to genetic testing in inherited muscle and neuromuscular junction disorders is guided by the patient's phenotype. First and foremost, clinicians must identify those whose phenotypes suggest a myopathy that requires targeted genetic testing (i.e., myotonic dystrophies, FSHD, OPMD, OPDM, DMD, and mitochondrial myopathies). In the remainder of patients, the best initial step is a gene panel encompassing a large number of genes related to myopathy and CMSs, and which also includes copy number variation analysis. (p. 264) The authors also recommend that "...genetic testing can also be considered in certain patients with asymptomatic CK [creatine kinase] elevations." (p. 261)

GeneReviews: Congenital Myasthenic Syndromes Overview

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.

An individual with a congenital myasthenic syndrome (CMS) typically presents with a history of fatigable weakness involving ocular, bulbar, and limb muscles with onset at or shortly after birth or in early childhood, usually in the first two years. Rarely, onset is in the second to third decade of life.

Neonatal presentation:

- Respiratory insufficiency with sudden, episodic apnea and cyanosis are common findings in neonates.
- Neonates with CMS can have multiple joint contractures (often described as arthrogryposis multiplex congenita) resulting from a lack of fetal movement in utero.
- Other major findings in the neonatal period may include feeding difficulties, poor suck and cry, choking spells, eyelid ptosis, and facial, bulbar, and generalized weakness. Stridor in infancy may be an important clue to CMS.
- In some individuals, long face, narrow jaw, and a high-arched palate have been reported.

Childhood presentation: Individuals with onset later in childhood show abnormal muscle fatigability, with difficulty in running or climbing stairs.

both eyelids.
- Facial and bulbar weakness with nasal speech and difficulties in coughing and swallowing may be present.
- Spinal deformity or muscle atrophy may occur.

Comprehensive Ataxia Panel

American College of Medical Genetics and Genomics (ACMG)

ACMG (2013, p. 673) stated the following in regard to "establishing the diagnosis of hereditary ataxia:

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.
Exclusion of nongenetic causes of ataxia.
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."

***SMN1* Sequencing and/or Deletion/Duplication Analysis and *SMN2* Deletion/Duplication Analysis**

GeneReviews: Spinal Muscular Atrophy

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 Spinal Muscular Atrophy are as follows:

Newborn Screening (NBS) for spinal muscular atrophy (SMA) is primarily based on real-time PCR that detects the common *SMN1* deletion and may also detect *SMN2* copy number on dried blood spots. Follow-up molecular genetic testing confirmation of a positive NBS result is recommended.

yielded a false negative result) molecular genetic testing approaches can include single-gene testing (*SMN1*) or use of a multigene panel that includes *SMN1*, *SMN2*, and other genes of interest.

- History of motor difficulties, especially with loss of skills
- Proximal > distal muscle weakness
- Hypotonia
- Areflexia/hyporeflexia
- Tongue fasciculations
- Hand tremor
- Recurrent lower respiratory tract infections or severe bronchiolitis in the first few months of life
- Evidence of motor unit disease on electromyogram

Gene-targeted deletion/duplication analysis to determine *SMN2* copy number can be performed to provide additional information for clinical correlation if the diagnosis of SMA is confirmed on molecular genetic testing.

***MECP2* Sequencing and/or Deletion/Duplication Analysis**

GeneReviews: MECP2 Disorders

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 clinical findings found in females with *MECP2* disorder (for both classic and variant Rett syndrome) include the following:

- Most distinguishing finding: A period of regression (range: ages 1-4 years) followed by recovery or stabilization (range ages 2-10 years; mean age 5 years)
- Main findings:
  - Partial or complete loss of acquired purposeful hand skills
  - Partial or complete loss of acquired spoken language or language skill (e.g., babble)
  - Gait abnormalities: impaired (dyspraxic) or absence of ability
  - Stereotypic hand movements including hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms
- Exclusionary findings
  - Brain injury secondary to peri- or postnatal trauma, neurometabolic disease, or severe infection that causes neurological problems
  - Grossly abnormal psychomotor development in the first six months of life, with early milestones not being met

National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy (Smith et al, 2022). The NSGC recommendations are as follows (page 4):

- Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age.
- Multi-gene, comprehensive testing, such as exome sequencing, genome sequencing or a multigene panel as a first-tier test is strongly recommended*

Per the practice guideline, the multi-gene panel should have a minimum of 25 genes and include copy number analysis. However, specific genes to be included in such panels were not outlined in the guidelines. For this reason, the number of genes included in the multi-gene panel was not added to the clinical coverage criteria. In rare situations, an epilepsy panel of fewer than 25 genes may be performed, in which case alternate coverage criteria should be used (please refer to Concert medical policy “General Approach to Genetic and Molecular Testing”).

NOTCH3 Sequencing and/or Deletion/Duplication Analysis

GeneReviews: CADASIL

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.

CADASIL [cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy] should be suspected in individuals with unexplained white matter hyperintensities and a family history of stroke and/or vascular dementia; however, lack of an apparent family history of CADASIL does not preclude the diagnosis. The following clinical signs and neuroimaging findings can be observed in CADASIL.

Clinical signs

- Transient ischemic attacks and ischemic stroke
- Cognitive impairment, manifesting initially with executive dysfunction, with a concurrent stepwise deterioration due to recurrent strokes to vascular dementia
- Migraine with aura, with a mean age of onset of 30 years
- Psychiatric disturbances, most frequently mood disturbances and apathy

involving the anterior temporal lobes and external capsules
- Lacunes of presumed vascular origin
- Recent subcortical infarcts
- Dilated perivascular spaces, sometimes referred to as subcortical lacunar lesions
- Brain atrophy
- Cerebral microbleeds

The diagnosis of CADASIL is established in a proband either by identification of a heterozygous pathogenic (or likely pathogenic) variant in *NOTCH3* by molecular genetic testing or, if molecular genetic testing is not definitive, by detection of characteristic findings by electron microscopy and immunohistochemistry of a skin biopsy.

PSEN1, _PSEN2_, and _APP_ Sequencing and/or Deletion/Duplication Analysis

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 a joint practice guideline, which was reaffirmed and reclassified as a practice resource in 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 [early-onset Alzheimer disease] 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*). (p. 601)

Alzheimer genetics is traditionally subdivided into early onset (EOAD) and late onset (LOAD). EOAD has an onset before age 60–65 years and accounts for 1–5% of all cases. LOAD has an onset after age 60–65 years and is the predominant form of AD (p. 598).

Ideally, an affected family member should be tested first. If no affected family member is available for testing and an asymptomatic individual remains

APOE Variant Analysis for Alzheimer's Disease

Food and Drug Administration (FDA)

In the "highlights of prescribing information" document created by the FDA for monoclonal antibodies treatment directed against aggregated forms of beta amyloid, including Leqembi, the following is recommended: "Patients treated with this class of medications, including Leqembi, who are ApoE e4 homozygotes have a higher incidence of ARIA [amyloid related imaging abnormalities], including symptomatic and serious ARIA, compared to heterozygotes and noncarriers. Testing for ApoE e4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA." (p. 1)

Amyotrophic Lateral Sclerosis (ALS) Multigene Panel

Roggenbuck, et al

The ALS Genetic Testing and Counseling Guidelines Expert Panel published evidence based consensus guidelines (2023) for genetic testing. They state that all persons with ALS should be offered a gene panel including C9orf72, *SOD1*, *FUS*, *TARDBP*, and additional genes strongly and definitively associated with ALS by ClinGen. (p. 6)

GeneReviews: Amyotrophic Lateral Sclerosis Overview

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 Amyotrophic Lateral Sclerosis are as follows:

It is estimated that about 10%-15% of individuals with ALS have genetic ALS. Some of the genetic forms of ALS may confer particular clinical characteristics, although intra- and interfamilial variability of age at onset and disease progression is common.

The diagnosis of ALS requires characteristic clinical features and specific findings on electrodiagnostic testing, as well as exclusion of other health conditions with related manifestations. Criteria for diagnosis include:

- The presence of all of the following:
  - Evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiologic, or neuropathologic examination

other regions, as determined by history or examination

Together with the absence of both of the following:

Electrophysiologic or pathologic evidence of other disease processes that could explain the signs of LMN and/or UMN degeneration

Neuroimaging evidence of other disease processes that could explain the observed clinical and electrophysiologic signs

Clinical evidence of UMN and LMN signs in the four regions of the central nervous system (i.e., brain stem, cervical, thoracic, or lumbosacral spinal cord) can be obtained through detailed or focused history and physical and neurologic examinations.

The following genes are listed as the most common genes causing ALS: *C9orf72, SOD1, FUS,* and *TARDBP.*

Diagnostic *DMD* Sequencing and/or Deletion/Duplication Analysis

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.” (p. 254)

disease, and goes through a rigorous editing and peer review process before being published online.

A dystrophinopathy should be suspected in an individual with the following clinical and laboratory test findings that support the diagnosis of DMD, BMD, or DMD-associated DCM – especially when they occur in addition to a positive family history compatible with X-linked inheritance. Findings are most commonly noted in males, but females may also be affected.

Duchenne muscular dystrophy (DMD)

- Progressive symmetric muscle weakness (proximal > distal) often with calf hypertrophy
- Symptoms present before age five years
- Wheelchair dependency before age 13 years

All patients with DMD have serum creatine phosphokinase levels that are greater than 10X normal values.

Becker muscular dystrophy (BMD):

- Progressive symmetric muscle weakness (proximal > distal) often with calf hypertrophy; weakness of quadriceps femoris in some cases the only sign
- Activity-induced cramping (present in some individuals)
- Flexion contractures of the elbows (if present, late in the course)
- Wheelchair dependency (after age 16 years); although some individuals remain ambulatory into their 30s and in rare cases into their 40s and beyond
- Preservation of neck flexor muscle strength (differentiates BMD from DMD)

All patients with BMD have serum creatine phosphokinase levels that are greater than 5X normal values.

D4Z4 Haplotype Analysis, and/or *SMCHD1* and *DNMT3B* Sequencing and/or Deletion/Duplication 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; reaffirmed in 2021) 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

obtain genetic confirmation of FSHD1 in patients with atypical presentations... (p. 360)

GeneReviews-Facioscapulohumeral Muscular Dystrophy

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.

Facioscapulohumeral muscular dystrophy (FSHD) should be suspected in individuals with the following:

- Weakness that predominantly involves the facial, scapular stabilizer, or foot dorsiflexor muscles without associated ocular or bulbar muscle weakness. Weakness is often asymmetric.
- Progression of weakness after pregnancy
- Prior diagnosis with inflammatory myopathy that was refractory to immunosuppression
- Family history of FSHD

Per GeneReviews, the diagnosis of FSHD1 is established in a proband with characteristic clinical features by identification of a heterozygous pathogenic contraction of the D4Z4 repeat array in the subtelomeric region of chromosome 4q35 on a chromosome 4 permissive haplotype. Molecular genetic testing for a heterozygous pathogenic variant in *SMCHD1* or *DNMT3B* can be pursued in individuals with at least one permissive chromosome 4 haplotype (e.g., 4A161, 4A159, 4A168, 4A166H) and hypomethylation of D4Z4.

FXN Repeat Analysis and/or Sequencing Analysis

American College of Medical Genetics

The American College of Medical Genetics (ACMG, 2013) states the following regarding testing for hereditary ataxias:

“Establishing the diagnosis of hereditary ataxia requires:

- 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.
- Exclusion of nongenetic causes of ataxia.
- Documentation of the hereditary nature of the disease by finding a positive family history of ataxia, identifying an ataxia-causing

"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." (p. 673)

GeneReviews: Friedreich Ataxia

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.

Friedreich ataxia (FRDA) should be suspected in individuals with a combination* of the following clinical features and family history:

- Neurologic findings, typically with onset before age 25 years**.
  - Progressive ataxia of gait and limbs
  - Dysarthria
  - Decrease in/loss of position sense and/or vibration sense in lower limbs ?
  - Pyramidal weakness of the legs, extensor plantar responses
- Musculoskeletal features
  - Muscle weakness
  - Scoliosis
  - Pes cavus
- Hypertrophic non-obstructive cardiomyopathy
- Endocrinologic features
  - Glucose intolerance
  - Diabetes mellitus
- Optic atrophy and/or deafness
- Family history consistent with autosomal recessive inheritance Note: Absence of a family history of autosomal recessive inheritance does not preclude the diagnosis.

NOTE: Concert interprets a combination of these clinical features, here, to mean at least two.

NOTE: In atypical cases, onset may be delayed

HTT Repeat Analysis

GeneReviews-Huntington Disease

being published online. The recommendations for genetic testing for Huntington disease are 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

Testing is performed by targeted analysis of CAG repeats within the *HTT* gene.

At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. In a family with an established diagnosis of HD, it is appropriate to consider testing of symptomatic individuals regardless of age.

Huntington's Disease Society of America (HDSA)

The Huntington's Disease Society of America (HDSA) established a protocol for safe and effective testing of Huntington's Disease, both in the predictive (asymptomatic) setting and for those who have symptoms. Specifically, they state that "confirmatory testing by analysis of the HD gene is offered at or after the time of the clinical diagnosis of HD. The presence of a CAG repeat expansion in a person with HD symptoms confirms the clinical impression and supports a diagnosis of HD". (p. 13) Additionally, it is stated that "minors should not undergo genetic testing unless there is a medically compelling reason such as a clinical diagnosis or a strong suspicion of HD". (p. 16)

National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC) issued a statement in 2018 which 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.

Panel

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.

GeneReviews: Charcot-Marie-Tooth Hereditary Neuropathy Overview

Individuals with CMT [Charcot-Marie-Tooth] manifest symmetric, slowly progressive distal motor neuropathy of the arms and legs usually beginning in the first to third decade and resulting in weakness and atrophy of the muscles in the feet and/or hands. 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).

"Establishing a specific genetic cause of CMT hereditary neuropathy can aid in discussions of prognosis …and genetic counseling."

GeneReviews: Hereditary Neuropathy with Liability to Pressure Palsies

Hereditary neuropathy with liability to pressure palsies (HNPP) should be suspected in individuals with the following clinical findings, electrophysiologic studies, imaging studies, and family history.

Typical clinical findings:

- 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

"The diagnosis of HNPP is established in a proband with suggestive findings by identification of either the 1.5-megabase (Mb) recurrent deletion or a novel deletion involving *PMP22* (in 80%), or a pathogenic (or likely pathogenic) *PMP22* sequence variant (in 20%) by molecular genetic testing."

Limb Girdle Muscular Dystrophy Multigene Panel

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

dystrophies. These guidelines included a systematic review, which identified common features of limb-girdle muscular dystrophy (LGMD) including slowly progressive symmetrical weakness. The age of onset is highly variable but usually adolescence to early adulthood.

The guidelines also note that although limb-girdle pattern of weakness affecting proximal muscles of the arms and legs is the most common presentation, other patterns, including scapuloperoneal weakness and distal weakness, are not rare. (p. 1454)

These guidelines note that “serum CK levels vary widely between patients with the same disorder, ranging from normal to greater than 10 times above normal levels, and can be as much as 100 times normal in some cases.” (p. 1455)

UpToDate: Limb-girdle Muscular Dystrophy

For patients suspected of having LGMD, broad genetic testing (rather than muscle biopsy), has become common. Testing should be obtained with an LGMD or neuromuscular gene panel, which contains multiple genes associated with LGMDs and other muscular dystrophies/myopathies.

DMPK and/or _CNBP_ (ZNF9) 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”. (p. 32)

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:

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." (page 22).

American College of Medical Genetics

ACMG published technical standards and guidelines for myotonic dystrophy type 1 in 2009 and reaffirmed in 2015. In it, they state: "Indications for genetic testing: This test is often used for symptomatic confirmatory diagnostic testing and predictive testing, after the identification of the mutation in an affected family member. (p. 553).

GeneReviews-Myotonic Dystrophy Type 1 and Myotonic Dystrophy Type 2

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. They suggest that Myotonic dystrophy type 1 (DM1) should be suspected in adults with the following:

- Muscle weakness, especially of the distal leg, hand, neck, and face
- Myotonia (sustained muscle contraction), which often manifests as the inability to quickly release a hand grip (grip myotonia)
- Posterior subcapsular cataracts detectable as red and green iridescent opacities on slit lamp examination

DM1 should be suspected in neonates with some combination of the following:

- Hypotonia
- Facial muscle weakness
- Generalized weakness
- Positional malformations including clubfoot
- Respiratory insufficiency

DM2 should be suspected in individuals with the following findings:

- Muscle weakness
- Myotonia (sustained muscle contraction) that can manifest as:
  - grip myotonia (the inability to release a tightened fist quickly) occurring as early as the first decade of life
  - percussion myotonia (sustained contraction after tapping a muscle with a reflex hammer)

observed on EMG).

Note: The myotonia in individuals with DM2 is not always detectable by EMG and may require an extensive EMG examination of several muscle groups including proximal and paraspinal muscles

Posterior subcapsular cataracts detectable as nonspecific vacuoles and opacities on direct ophthalmoscopy or as pathognomonic posterior subcapsular red and green iridescent opacities on slit lamp examination

Cardiac conduction defects or progressive cardiomyopathy

Insulin insensitivity

Hypogammaglobulinemia

“For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.”

Hereditary Dystonia Multigene Panel

GeneReviews-Hereditary Dystonia Overview

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.

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.

Parkinson Disease Multigene Panel

GeneReviews - Parkinson Disease Overview

Per the Parkinson Disease GeneReviews, establishing a specific genetic cause of Parkinson disease:

- Can aid in discussions of causation, recurrence risks, and research eligibility.
- May provide some information about phenotype including prognosis of a particular monogenic cause of Parkinson disease.
- Usually involves evaluation of medical and family histories, and molecular genetic testing. Physical examination may be less helpful in suggesting a specific genetic cause because of the overlap of clinical features.

Gasser et al (2023)

This review article states the following: “The identification of disease-causing mutations or strong risk factors for Parkinson’s disease in genes encoding proteins such as α-synuclein (*SNCA*), leucine-rich repeat kinase-2 (*LRRK2*), or glucocerebrosidase (*GBA1*) has led to a better understanding of the different components of disease pathogenesis. Many gene and mutation-specific targeted disease-modifying treatments are under development and several studies are underway. It is, therefore, important to raise awareness among patients and their families and to offer genetic testing, at least to those patients who are considering to participate in innovative trials.” (p. 777)

Hereditary Spastic Paraplegia Multigene Panel

GeneReviews-Hereditary Spastic Paraplegia Overview

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 predominant signs and symptoms of hereditary spastic paraplegia (HSP) are lower-extremity weakness and spasticity. Individuals with HSP demonstrate the following:

- Bilateral lower-extremity spasticity (especially in hamstrings, quadriceps, adductors, and gastrocnemius-soleus muscles)
- Weakness (especially 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

identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype.

Congenital Myasthenic Syndromes Multigene Panel

GeneReviews-Congenital Myasthenic Syndromes Overview

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.

GeneReviews comments on the onset of myasthenic syndromes as follows:

- Neonatal presentation: Some myasthenic symptoms are present at birth. Symptoms include:
  - Respiratory insufficiency with sudden, episodic apnea and cyanosis are common findings in neonates.
  - Neonates with CMS can have multiple joint contractures (often described as arthrogryposis multiplex congenita) resulting from a lack of fetal movement in utero.
  - Other major findings in the neonatal period may include feeding difficulties, poor suck and cry, choking spells, eyelid ptosis, and facial, bulbar, and generalized weakness. Stridor in infancy may be an important clue to CMS.
  - In some individuals, long face, narrow jaw, and a high-arched palate have been reported.
- Childhood presentation: Individuals with onset later in childhood show abnormal muscle fatigability, with difficulty in running or climbing stairs. Symptoms include:
  - Motor milestones may be delayed.
  - Affected individuals present with fluctuating eyelid ptosis and fixed or fluctuating extraocular muscle weakness. Ptosis may involve one or both eyelids.
  - Facial and bulbar weakness with nasal speech and difficulties in coughing and swallowing may be present.
  - Spinal deformity or muscle atrophy may occur.

An individual with a congenital myasthenic syndrome (CMS) typically presents with a history of fatigable weakness involving ocular, bulbar, and limb muscles with onset at or shortly after birth or in early childhood, usually in the first two years. Rarely, onset is in the second to third decade of life.

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.

Per GeneReviews, there are no consensus clinical diagnostic criteria for myotonia congenita (sometimes referred to as "chloride channel myotonia") that have been published. Myotonia congenita should be suspected in individuals with the following clinical and laboratory findings:

Clinical findings and medical history

- Episodes of muscle stiffness (myotonia) or cramps beginning in early childhood
- Alleviation of stiffness by brief exercise (known as the "warm-up" effect)
- Myotonic contraction elicited by percussion of muscles

Laboratory findings

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

Myotonia Congenita - National Institutes of Health (NIH)

In this review of Myotonia Congenita (MC), the authors state the following:

Genetic testing is considered the gold standard. Biochemical investigations are usually unremarkable, although mild elevations of creatinine kinase have been described up to three to four times the upper limit of normal. Electromyography is a useful tool in the diagnosis of MC however, it is time-consuming, uncomfortable, and results in an overlap between the different channelopathies. There is no electromyographical difference between the two types of MC. Given the widespread availability of genetic testing, muscle biopsy is now rarely performed, but it may show heterogeneous muscle fibers with increased numbers of nuclei and absent type 2B fibers. A muscle biopsy is not necessary to establish a diagnosis of MC.

CACNA1S and _SCN4A_ Sequencing and/or Deletion/Duplication Analysis, or Periodic Paralysis Multigene Panel

GeneReviews - Hypokalemic Periodic Paralysis

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.

Two or more attacks of muscle weakness with documented serum potassium less than 3.5 mEq/L
OR
One attack of muscle weakness in the proband and one attack of weakness in one relative with documented serum potassium less than 3.5 mEq/L
OR
Three or more of the following six clinical/laboratory features:
- Onset in the first or second decade
- Duration of attack (muscle weakness involving at least 1 limbs) longer than two hours
- The presence of triggers (previous carbohydrate rich meal, symptom onset during rest after exercise, stress)
- Improvement in symptoms with potassium intake
- A family history of the condition or genetically confirmed skeletal calcium or sodium channel mutation
- Positive long exercise test AND

Exclusion of other causes of hypokalemia (renal, adrenal, thyroid dysfunction; renal tubular acidosis; diuretic and laxative abuse)

When the phenotypic and laboratory findings suggest the diagnosis of hypoPP, the recommended approach is the use of a multigene panel.

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REVISIONS

12-04-2024
Updated policy/version for 01/01/2025

12-04-2023
Updated policy for 01/01/2024

09-27-2023
Changed "may be considered medically necessary" to "may be considered scientifically validated"

Added: "investigational when the above criteria is not met and for all other indications"

06-01-2023
Criteria update: Inherited Peripheral Neuropathies, references and formatting changes

06-09-2022
Updated criteria for SCN1a Seizure Disoders, PSEN1, PSEN2, and APP criteria, and PMP22 sequencing and/or deletion/duplication critiera for effective date of 07/0/2022

03-01-2022
Updated codes, criteria and references effective 3/1/2022

08-24-2021
Added 81419

07-21-2021
Removed 81329

03-23-2021
Added new 01/01/2021 code: 0230U, 0236U