Medica Central Coverage Policy

Policy Name:	**Genetic Testing - Specialty Testing: Neurology**
Effective Date:	**01/01/2026**

Important Information – Please Read Before Using This Policy
These services may or may not be covered by all Medica Central plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless these programs require different coverage.
Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions may call the Provider Service Center. Please use the Quick Reference Guide on the Provider Communications page for the appropriate phone number.

https://mo-central.medica.com/Providers/SSM-employee-health-plan-for-IL-MO-OK-providers

Medica Central coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment.
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OVERVIEW

This policy addresses the use of tests for evaluation for neurological conditions.

For additional information see the Rationale and References section.

The tests, CPT codes, and ICD codes referenced in this policy are not comprehensive, and their inclusion does not represent a guarantee of coverage or non-coverage. Please see the Concert Platform for additional registered tests.

POLICY REFERENCE TABLE

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
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	Rationale/ References
	Comprehensive Neuromuscular Disorders Panel (Invitae Corporation)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	Neuromuscular Disorders Panel (GeneDx)		
Comprehensive Ataxia Panel			
Comprehensive Ataxia Panel	Genomic Unity Ataxia Repeat Expansion Analysis - 0216U (Variantyx, Inc.)	81185, 81189, 81286, 81403, 81404, 81479, 0216U, 0217U, G11.1, G11.19, G11.8, G11.9, Z82.0	Rationale/ References
	Genomic Unity Comprehensive Ataxia Analysis - 0217U (Variantyx, Inc.)		
	Ataxia Xpanded Panel (GeneDx)		
Spinal Muscular Atrophy			
SMN1 Sequencing and/or Deletion/Duplication Analysis	Spinal Muscular Atrophy (SMA), Diagnostic (Quest Diagnostics)	81329, 81336, 81405, 0236U, G12, Z84.81	Rationale/ References
	SMN1 Sequencing and Deletion/Duplication Analysis (Fulgent Genetics)		
	Genomic Unity *SMN1/2* Analysis - 0236U (Variantyx Inc.)		
SMN2 Deletion/Duplication Analysis	*SMN2* Deletion/Duplication (GeneDx)	81401, G12, Z84.81	Rationale/ References
Rett Syndrome			
MECP2 Sequencing and/or Deletion/Duplication Analysis	*MECP2* Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)	81302, 81304, 0234U, F70-F79, F80, F81, F82, F84, F88, F89, Z13.4, Z82.79, Z84	Rationale/ References
	MECP2 Gene Sequencing & Del/Dup (GeneDx)		
	Genomic Unity *MECP2* Analysis - 0234U (Variantyx, Inc.)		
Epilepsy			

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Epilepsy Multigene Panel	Comprehensive Epilepsy Panel (Blueprint Genetics)	81185, 81189, 81302, 81406, 81419, 81479, G40.001- G40.919	Rationale/ References
	Comprehensive Epilepsy Panel (GeneDx)		
	Clinical Epilepsy NGS Panel (LabCorp)		
	EpilepsyNext (Ambry Genetics)		
	Epilepsy Panel (Invitae Corporation)		
Alzheimer's Disease			
PSEN1, *PSEN2*, and *APP* Sequencing and/or Deletion/Duplication Analysis	*PSEN1* Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)	81405, 81406, 81479, F03, G30, G31.1, R41.0, R41.81, Z13.858, Z82.0, Z84.81	Rationale/ References
	Alzheimer's Disease, Familial via the *PSEN2* Gene (PreventionGenetics, part of Exact Sciences)		
	APP Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)		
	Alzheimer's Disease, Familial, Panel (PreventionGenetics, part of Exact Sciences)		
	Hereditary Alzheimer's Disease Panel (Invitae Corporation)		
APOE Variant Analysis for Alzheimer's Disease	APOE Alzheimer's Disease Risk (LabCorp)	81401, 81479, S3852, F03, G30, G31.1, R41.0, R41.81, Z13.858, Z82.0, Z84.81	Rationale/ References
Amyotrophic Lateral Sclerosis (ALS)			
Targeted *C9orf72* Repeat Expansion Testing and Amyotrophic Lateral	Amyotrophic Lateral Sclerosis (ALS) Panel (PreventionGenetics, part	81179, 81403, 81404, 81405, 81406, 81407, 81479, S3800, G12.21	Rationale/ References

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Sclerosis (ALS) Multigene Panels	of Exact Sciences)		
	Amyotrophic Lateral Sclerosis Panel (Invitae Corporation)		
Duchenne and Becker Muscular Dystrophy			
Diagnostic *DMD* Sequencing and/or Deletion/Duplication Analysis	Dystrophinopathies Test (Invitae Corporation)	81161, 81408, 0218U, G71.01, R62.59, Z84.81	Rationale/ References
	Duchenne/Becker MD (DMD) Gene Sequencing (GeneDx)		
	Genomic Unity DMD Gene Analysis - 0218U (Variantyx, Inc.)		
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 (University of Pennsylvania School of Medicine - Molecular Pathology Laboratory)	81404, 81479, G71.02, Z84.81	Rationale/ References
	Facioscapulohumeral Muscular Dystrophy 2 via the *SMCHD1* Gene (PreventionGenetics, part of Exact Sciences)		
	DNMT3B Full Gene Sequencing And Deletion/Duplication (Invitae Corporation)		
	FSHD-(FSHD1 & FSHD2) Detection of Abnormal Alleles with Interpretation (University of Iowa Hospitals and Clinics - Department of Pathology)		
Friedreich's Ataxia			
FXN Repeat Analysis and/or Sequencing	Friedreich Ataxia (*FXN*) Repeat Expansion Test	81284, 81285, 81286, 81404, 0233U, G11,	Rationale/ Reference

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Analysis	(Athena Diagnostics, Inc.)	Z84.81	s
	Friedreich Ataxia (*FXN*) DNA Sequencing Test (Athena Diagnostics, Inc.)		
	Genomic Unity *FXN* Analysis - 0233U (Variantyx, Inc.)		
Huntington's Disease (HD)			
HTT Repeat Analysis	Huntington Disease (*HTT*) Genetic Testing (Repeat Expansion) (LabCorp)	81271, 81274, G10, Z84.81	Rationale/ References
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, 81325, 81448, G60.0, G60.8, G60.9	Rationale/ References
	PMP22 DNA Sequencing Test (Quest Diagnostics)		
	Charcot-Marie Tooth (CMT) - Comprehensive Panel (PreventionGenetics, part of Exact Sciences)		
	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	Rationale/ References
	Limb-Girdle Muscular Dystrophy Panel (Invitae Corporation)		
Myotonic Dystrophy			
DMPK and/or *CNBP* (*ZNF9*) Repeat Analysis	Myotonic Dystrophy 1 (*DMPK*) Genetic Testing (Repeat Expansion) (LabCorp)	81187, 81234, 81239, 81401, 81404, S3853, G71.11, Z84.81	Rationale/ References

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	Myotonic Dystrophy 2 (*ZNF9 / CNBP*) Genetic Testing (Repeat Expansion) (LabCorp)		
Hereditary Dystonia			
Hereditary Dystonia Multigene Panel	Dystonia Panel (GeneDx)	81404, 81405, 81406, 81407, 81408, 81479, G24.1, G24.9	Rationale/ References
	Dystonia Panel (PreventionGenetics, part of Exact Sciences)		
	Dystonia Comprehensive Panel (Invitae Corporation)		
Parkinson's Disease			
Parkinson's Disease Multigene Panel	Parkinson Disease Panel (Blueprint Genetics)	81479, G20	Rationale/ References
	Parkinson Disease Panel (GeneDx)		
	Invitae Parkinson Disease and Parkinsonism Panel (Invitae Corporation)		
Hereditary Spastic Paraplegia			
Hereditary Spastic Paraplegia Multigene Panel	Spastic Paraplegia Panel (Blueprint Genetics)	81448, G11.4, G82.2	Rationale/ References
	Hereditary Spastic Paraplegia Comprehensive Panel (Invitae Corporation)		
Congenital Myasthenic Syndrome			
Congenital Myasthenic Syndromes Multigene Panel	Congenital Myasthenic Syndrome Panel (PreventionGenetics, part of Exact Sciences)	81405, 81406, 81407, 81479, G70.2	Rationale/ References
	Congenital Myasthenic Syndrome Panel (Invitae Corporation)		
Myotonia Congenita			

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
CLCN1 Sequencing and/or Deletion/Duplication Analysis	Myotonia Congenita via the *CLCN1* Gene (PreventionGenetics, part of Exact Sciences)	81406, 81479, G71.1, G71.12	Rationale/ References
	CLCN1 Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)		
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 Corporation)	81185, 81406, 81479, E87.6, G72.3	Rationale/ References
	SCN4A Full Gene Sequencing and/or Deletion/Duplication (Invitae Corporation)		
Other Covered Epilepsy, Neuromuscular, and Neurodegenerative Disorders			
Other Covered Epilepsy, Neuromuscular, and Neurodegenerative Disorders	See list below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479	Additional References

RELATED POLICIES

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

- ***Reproductive Testing: Prenatal Diagnosis*** for coverage criteria related to fetal diagnostic testing for genetic disorders during pregnancy.
- ***Reproductive Testing: Carrier Screening*** for coverage criteria related to parental carrier screening for genetic disorders before or during pregnancy.
- ***Specialty Testing: Toxicology and Pharmacogenetics*** for coverage criteria related to drug and treatment response and toxicity testing.
- ***Specialty Testing: Multisystem Genetic Conditions*** for coverage criteria related to diagnostic tests for genetic disorders that affect multiple organ systems (e.g. whole exome and genome sequencing, chromosomal microarray, and multigene panels for broad phenotypes).
- ***Reproductive Testing: Fertility*** for coverage criteria related to preimplantation diagnosis.

- ***Specialty Testing: Cardiology*** for coverage criteria related to dilated cardiomyopathy, including *DMD*-related dilated cardiomyopathy.
- ***General Approach to Laboratory Testing*** or coverage criteria related to neurology, including known familial variant testing, that is not specifically discussed in this or another non-general policy.

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COVERAGE CRITERIA

COMPREHENSIVE NEUROMUSCULAR DISORDERS PANEL

Comprehensive Neuromuscular Disorders Panel

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

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.

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

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COMPREHENSIVE ATAXIA PANEL

Comprehensive Ataxia Panel

I. Comprehensive ataxia panel analysis to establish a genetic diagnosis of an ataxia 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 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 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 to establish or confirm a diagnosis of spinal muscular atrophy (SMA) is considered **investigational** for all other indications.

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SMN2 Deletion/Duplication Analysis

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

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

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

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RETT SYNDROME

MECP2 Sequencing and/or Deletion/Duplication Analysis

I. *MECP2* sequencing and/or deletion/duplication analysis 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 to establish or confirm a diagnosis of Rett syndrome is considered **investigational** for all other indications.

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EPILEPSY

Epilepsy Multigene Panel

I. The use of an epilepsy multigene panel 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, structural brain abnormality, and/or stroke).

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

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ALZHEIMER'S DISEASE

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

I. *PSEN1*, *PSEN2*, and/or *APP* sequencing and/or deletion/duplication analysis to establish a diagnosis or determine future risk to develop early-onset Alzheimer's 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[1], **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's 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.**[2]

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

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

[2] Please see clinical guidelines *APOE* Variant Analysis for Alzheimer's Disease for coverage criteria for *APOE* testing

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APOE Variant Analysis for Alzheimer's Disease

I. *APOE* variant analysis 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 is considered **investigational** for all other indications.

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AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Targeted _C9orf72_ Repeat Expansion Testing and Amyotrophic Lateral Sclerosis (ALS) Multigene Panels

I. Targeted *C9orf72* hexanucleotide repeat expansion testing and multigene panel analysis to establish a genetic etiology of amyotrophic lateral sclerosis (ALS) 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.

II. Targeted *C9orf72* hexanucleotide repeat expansion testing and multigene panel analysis to establish a genetic etiology of amyotrophic lateral sclerosis (ALS) is considered **investigational** for all other indications.

NOTE: *C9orf72* hexanucleotide repeat expansion testing is typically done using a specialized method that may be performed as a standalone test, in parallel with, or as a reflex from multigene panel testing for ALS.

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DUCHENNE AND BECKER MUSCULAR DYSTROPHY

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

I. *DMD* sequencing and/or deletion/duplication analysis 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. Elevated serum creatine kinase concentration (greater than 2,000 IU/L), **AND**

a) At least one of the following:

(1) Muscle weakness, usually proximal greater than distal, **OR**

(2) Calf pseudohypertrophy, **OR**

(3) Delayed walking, **OR**

(4) Difficulty climbing or descending stairs, **OR**

(5) Difficulty running or walking, **OR**

(6) Frequent falls, **OR**

(7) Toe walking, **OR**

(8) Gower maneuver or difficulty rising from the floor, **OR**

(9) Elevated transaminases, **OR**

B. The member has all of the following clinical characteristics of BMD:

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.

II. *DMD* sequencing and/or deletion/duplication analysis 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)

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

I. D4Z4 haplotype analysis, and/or *SMCHD1* and *DNMT3B* sequencing and/or deletion/duplication analysis or multigene panel analysis to establish or confirm a diagnosis of facioscapulohumeral muscular dystrophy is considered **medically necessary** when:

A. The member displays any of the following:

1. Weakness (which is often asymmetric) that predominantly involves the facial, scapular stabilizer, or foot dorsiflexor muscles without associated ocular 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, and/or *SMCHD1* and *DNMT3B* sequencing and/or deletion/duplication analysis or multigene panel analysis 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 and/or Sequencing Analysis**

I. *FXN* repeat analysis and/or sequencing analysis 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**

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

B. The member is asymptomatic[1], **AND**

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

II. *FXN* repeat analysis and/or sequencing analysis to establish or confirm a diagnosis of Friedreich's Ataxia is considered **investigational** for all other indications.

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

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HUNTINGTON'S DISEASE (HD)

HTT Repeat Analysis

I. *HTT* repeat analysis to establish a diagnosis or for predictive testing of Huntington's disease (HD) 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[1], **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) is considered **investigational** for all other indications.

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

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

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

I. *PMP22* sequencing and/or deletion/duplication analysis or multigene panel analysis 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 or multigene panel analysis to establish a genetic diagnosis of an inherited peripheral neuropathy is considered **investigational** for all other indications.

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LIMB-GIRDLE MUSCULAR DYSTROPHIES (LGMD)

Limb-Girdle Muscular Dystrophy Multigene Panel

I. Multigene panel analysis to establish a diagnosis of limb-girdle muscular dystrophy is considered **medically necessary** when:

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

1. The member displays slowly progressive, symmetrical weakness, **AND**

2. The member has any of the following features:

a) Limb-girdle pattern of weakness affecting proximal muscles of the arms and legs, **OR**

b) Scapuloperoneal weakness, **OR**

c) Distal weakness, **OR**

d) Elevated serum creatine kinase levels, **OR**

B. 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 is considered **investigational** for all other indications.

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MYOTONIC DYSTROPHY

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

I. *DMPK* repeat analysis and/or *CNBP* repeat analysis 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, **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.

II. *DMPK* repeat analysis and *CNBP* repeat analysis 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 is considered **medically necessary** when:

A. The member has a clinical presentation consistent with dystonia or patterns of abnormal, repetitive, dystonic movements.

II. Multigene panel analysis to establish a genetic diagnosis of hereditary dystonia is considered **investigational** for all other indications.

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PARKINSON'S DISEASE

Parkinson's Disease Multigene Panel

I. Multigene panel testing to establish a genetic diagnosis of Parkinson's disease is considered **medically necessary** when:

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

   B. The member has a family history of Parkinson's disease.

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

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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 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 is considered **investigational** for all other indications.

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CONGENITAL MYASTHENIC SYNDROME

Congenital Myasthenic Syndromes Multigene Panel

I. Multigene panel analysis to establish a genetic diagnosis of congenital myasthenic syndromes 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 neonates, **OR**
4. Abnormal muscle fatigability/weakness, **OR**
5. Delayed motor milestones, **OR**
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 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 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 to establish a genetic diagnosis of myotonia congenita is considered **investigational** for all other indications.

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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 a periodic paralysis multigene panel to establish a genetic diagnosis of periodic paralysis is considered **medically necessary** when:

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

1. Two or more attacks of muscle weakness with documented serum potassium less than 3.5 mEq/L, **OR**

2. One attack of muscle weakness, **AND**

a) Has a close relative who has had one attack of muscle weakness with documented serum potassium less than 3.5 mEq/L, **OR**

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

a) Onset of symptoms within the first or second decade of life, **OR**

b) Muscle weakness involving at least 1 limb lasting longer than two hours, **OR**

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

d) Improvement in symptoms with potassium intake, **OR**

e) A clinical or genetic diagnosis of hypokalemic periodic paralysis in a close relative, **OR**

f) Positive long exercise test, **AND**

B. 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, or a periodic paralysis multigene panel 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

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 (*DDC*)

B. Hereditary Transthyretin Amyloidosis (*TTR)*

C. X-linked Adrenoleukodystrophy (*ABCD1*)

D. L1 Syndrome (*L1CAM*)

E. *SCN9A* Neuropathic Pain Syndromes

F. Cerebral Cavernous Malformation, Familial (*CCM2, KRIT1, PDCD10*)

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 Laboratory 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.

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PRIOR AUTHORIZATION

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

RATIONALE AND REFERENCES

Comprehensive Neuromuscular Disorders Panel

American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM)

In 2016, the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) developed a position statement 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).

Kassardjian CD, Amato AA, Boon AJ, Childers MK, Klein CJ; AANEM Professional Practice Committee. The utility of genetic testing in neuromuscular disease: A consensus statement from the AANEM on the clinical utility of genetic testing in diagnosis of neuromuscular disease. Muscle Nerve. 2016;54(6):1007-1009. doi:10.1002/mus.25387

Winder, et al.

In 2020, Winder, et al. published a study 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 test cannot be confidently selected because of a mild or uncharacteristic phenotype” (p. 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” (p. 7).

Winder TL, Tan CA, Klemm S, et al. Clinical utility of multigene analysis in over 25,000 patients with neuromuscular disorders. Neurol Genet. 2020;6(2):e412. Published 2020 Mar 9. doi:10.1212/NXG.0000000000000412

Nicolau, et al.

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).

Nicolau S, Milone M, Liewluck T. Guidelines for genetic testing of muscle and neuromuscular junction disorders. Muscle Nerve. 2021 Sep;64(3):255-269. Epub 2021 Jun 16. PMID: 34133031. doi:10.1002/mus.27337.

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 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.

- 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.

Abicht A, Müller JS, Lochmüller H. Congenital Myasthenic Syndromes Overview. 2003 May 9 [Updated 2021 Dec 23]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1168/

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Comprehensive Ataxia Panel

Jayadev, et al.

In 2013, Jayadev, et al. published an overview of hereditary ataxias and 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." (p. 673).

The article recommends molecular genetic testing in an individual who is suspected to have hereditary ataxia, and states that "Because of extensive clinical overlap among all of the forms of hereditary ataxia, it is difficult... to establish a diagnosis without molecular genetic testing" (p. 679).

Additionally, the articles states: "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).

Jayadev S, Bird TD. Hereditary ataxias: overview. Genet Med. 2013;15(9):673-683. doi:10.1038/gim.2013.28

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***SMN1* Sequencing and/or 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.

- A symptomatic individual who has EITHER atypical findings associated with later-onset SMA OR infantile-onset SMA that has not been treated (either because NBS was not performed or because it 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.

Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. 2000 Feb 24 [Updated 2024 Sept 19]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1352/.

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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:

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.

Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. 2000 Feb 24 [Updated 2024 Sept 19]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1352/.

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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.

Kaur S, Christodoulou J. MECP2 Disorders. 2001 Oct 3 [Updated 2019 Sep 19]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1497/

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Epilepsy Multigene Panel

National Society of Genetic Counselors (NSGC)

The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy. 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”).

Smith L, Malinowski J, Ceulemans S, et al. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. J Genet Couns. 2023;32(2):266-280. doi:10.1002/jgc4.1646

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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)

In 2011, ACMG and NSGC issued a joint practice guideline, which was reaffirmed and reclassified as a practice resource in 2019. These guidelines state that:

- Pediatric testing for Alzheimer’s disease (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 AD] 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).

AD 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 interested in testing despite counseling about the low likelihood of an informative result (a positive result for a pathogenic mutation), they should be counseled according to the recommended protocol (p. 601).

Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors [published correction appears in Genet Med. 2011 Aug;13(8):749]. Genet Med. 2011;13(6):597-605. doi:10.1097/GIM.0b013e31821d69b8

Goldman JS, Hahn SE, Catania JW, et al. ADDENDUM: Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. 2019;21(10):2404. doi:10.1038/s41436-019-0559-1

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APOE Variant Analysis for Alzheimer’s Disease

Food and Drug Administration (FDA)

The FDA drug labels for monoclonal antibody treatment, including both Leqembi and Kisunla, state that ApoE e4 testing should be completed prior to treatment initiation due to the increased incidence of ARIA (amyloid related imaging abnormalities), including symptomatic and serious ARIA in ApoE e4 homozygotes, compared to heterozygotes and noncarriers (p.1).

U.S. Food and Drug Administration. Labeling for Leqembi. FDA website. Approved January 6, 2023. Updated January 24, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761269s005lbl.pdf

U.S. Food and Drug Administration. Highlights of Prescribing Information: KISUNLA (donanemab-azbt), intravenous injection; FDA website. Approved 2024. Revised July 2024. https://www.fda.gov/media/180803/download

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Targeted *C9orf72* Repeat Expansion Testing and Amyotrophic Lateral Sclerosis (ALS) Multigene Panels

Roggenbuck, et al.

The ALS Genetic Testing and Counseling Guidelines Expert Panel has 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).

Roggenbuck J, Eubank BHF, Wright J, et al.; ALS Genetic Testing and Counseling Guidelines Expert Panel. Evidence-based consensus guidelines for ALS genetic testing and counseling [published online ahead of print, 2023 Sep 10]. Ann Clin Transl Neurol. 2023;10.1002/acn3.51895. doi:10.1002/acn3.51895

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:

Approximately 10%-15% of individuals with ALS have a genetic form of the disease. Some of these genetic forms may confer specific clinical characteristics, although intra- and interfamilial variability of features such as age at onset and disease progression is common.

Diagnosing ALS requires characteristic clinical features and specific findings on electrodiagnostic testing. It also requires excluding other health conditions with similar 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
    - Evidence of upper motor neuron (UMN) degeneration by clinical examination
    - Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination, AND

- 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.*

Siddique N, Siddique T. Amyotrophic Lateral Sclerosis Overview. 2001 Mar 23 [Updated 2023 Sept 28]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1450/

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

DMD Care Considerations Working Group

In 2018, the DMD Care Considerations Working Group, 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).

Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management [published correction appears in Lancet Neurol. 2018 Apr 4;:]. Lancet Neurol. 2018;17(3):251-267. doi:10.1016/S1474-4422(18)30024-3

GeneReviews: Dystrophinopathies

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.

This review lists the following clinical features as characteristic of 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)

The article goes on to state that all patients with BMD have serum creatine phosphokinase levels that are greater than 5X normal values."

Darras BT, Urion DK, Ghosh PS. Dystrophinopathies. 2000 Sep 5 [Updated 2022 Jan 20]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1119/

Food and Drug Administration (FDA)

There are multiple FDA-approved antisense oligonucleotide therapies for use in patients with a known pathogenic variant in the DMD gene.

U.S Food and Drug Administration. Query. FDA Label Database. Accessed May 28, 2025. https://nctr-crs.fda.gov/fdalabel/ui/spl-summaries/criteria/840392

Aartsma-Rus, et al.

A 2019 consensus guideline endorsed by multiple US and international medical societies recommends an algorithm to ensure timely diagnosis and treatment of Duchenne muscular dystrophy. The algorithm includes "calf hypertrophy (pseudohypertrophy); delayed walking; difficulty climbing/descending stairs; difficulty rising from the floor; difficulty running/walking; elevated serum CK levels (including elevated ALT and AST); a family history of DMD; frequent falls; Gowers' sign; male sex; and muscle weakness" as characteristic features of DMD that should prompt evaluation of serum creatinine kinase (CK).

Individuals with any of these signs and an elevated (>2,000 IU/L) serum CK are recommended to have germline genetic testing starting with deletion/duplication and, if uniformative, sequencing of the *DMD* gene (pp. 307, 309).

Aartsma-Rus A, Hegde M, Ben-Omran T, et al. Evidence-Based Consensus and Systematic Review on Reducing the Time to Diagnosis of Duchenne Muscular Dystrophy. J Pediatr. 2019;204:305-313.e14. doi:10.1016/j.jpeds.2018.10.043

National Society of Genetic Counselors (NSGC)

A 2024 practice resource for genetic counseling in dystrophinopathies lists “muscle weakness, delayed motor milestones, difficulty running and climbing stairs, and toe walking” as the most common presenting symptoms of dystrophinopathies. The Gower maneuver, calf pseudohypertrophy, and elevated transaminases are also included as symptoms that should prompt evaluation for dystrophinopathy (p. 7).
The resource states that serum creatinine kinase (CK) is typically over 2,000 IU/L in individuals with Duchenne or Becker muscular dystrophy (p. 7).

Pickart AM, Martin AS, Gross BN, et al. Genetic counseling for the dystrophinopathies-Practice resource of the National Society of Genetic Counselors. J Genet Couns. 2025;34(1):e1892. doi:10.1002/jgc4.1892

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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 2024) 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. In the setting of atypical or sporadic cases, genetic confirmation is important for genetic counseling, especially with the recent discovery of 2 genetically distinct forms of FSHD. They recommend that clinicians should obtain genetic confirmation of FSHD1 in patients with atypical presentations (p. 360).

Tawil R, Kissel JT, Heatwole C, et al. Evidence-based guideline summary: Evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology. 2015 (Reaffirmed July 2024);85(4):357-364. doi:10.1212/WNL.0000000000001783

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.

Preston MK, Tawil R, Wang LH. Facioscapulohumeral Muscular Dystrophy. 1999 Mar 8 [Updated 2020 Feb 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1443/

Facioscapulohumeral Muscular Dystrophy (FSHD) European Trial Network

The FSHD European Trial Network working group (which includes a US-based expert) published a 2024 update to previous guidelines describing genetic diagnosis for FSHD. This update includes a description of clinical findings associated with FSHD, including slowly progressing symptoms affecting primarily muscles of the face, shoulders, and upper arms, usually asymmetrically. In addition, many patients have weakness of trunk and leg muscles that sometimes may be the initial manifestations. There is marked variation in clinical manifestations, ranging from a severe early-onset form with higher incidence of nonmuscular features to asymptomatic or pauci-symptomatic presentations (p. 14). Specific clinical signs and features include: facial weakness and asymmetry, horizontal axillary fold, wasting of humeral muscles, drop foot, Beevor sign, poly-hill sign, winging and overriding scapula, lumbar hyperlordosis, hamstring weakness, and calf atrophy (p. 15).

Giardina E, Camaño P, Burton-Jones S, et al. Best practice guidelines on genetic diagnostics of facioscapulohumeral muscular dystrophy: Update of the 2012 guidelines. Clin Genet. 2024;106(1):13-26. doi:10.1111/cge.14533

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FXN Repeat Analysis and/or Sequencing Analysis

American College of Medical Genetics and Genomics (ACMG)

In 2013, ACMG stated 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 mutation, or recognizing a clinical phenotype characteristic of a genetic form of ataxia” (p. 673).

“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).

Jayadev S, Bird TD. Hereditary ataxias: overview. Genet Med. 2013;15(9):673-683. doi:10.1038/gim.2013.28

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[1] of the following clinical features and family history:

- Neurologic findings, usually with onset before age 25 years (Note: in atypical cases, onset may be at a later age):
    - Progressive ataxia of gait and limbs
    - Dysarthria (difficulty speaking due to muscle weakness)
    - 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 (high arches in the feet)
- 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 rule out a diagnosis.

[1]Concert interprets a combination of these clinical features, here, to mean at least two.

Bidichandani SI, Delatycki MB. Friedreich Ataxia. 1998 Dec 18 [Updated 202517 Apr 10Jun 1]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1281/

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HTT Repeat Analysis

GeneReviews: Huntington Disease

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 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.

Caron NS, Wright GEB, Hayden MR. Huntington Disease. 1998 Oct 23 [Updated 2020 Jun 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1305/

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).

Huntingtons Disease Society of America (HDSA). Genetic Testing Protocol for Huntingtons Disease. 2016. http://hdsa.org/wp-content/uploads/2015/02/HDSA-Gen-Testing-Protocol-for-HD.pdf

National Society of Genetic Counselors (NSGC)

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.

Genetic Testing of Minors for Adult-Onset Conditions. Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/genetic-testing-of-minors-for-adult-onset-conditions Released February 15, 2017. Updated April 12, 2018.

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

GeneReviews: Charcot-Marie-Tooth Hereditary Neuropathy 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 recommended diagnostic testing for hereditary neuropathy is as follows:

Individuals with Charcot-Marie-Tooth (CMT) display symmetric, progressing distal motor neuropathy of the extremities typically beginning in the first to third decade, which results in weakness and atrophy of the muscles in the feet and/or hands. Affected people typically have distal muscle weakness and atrophy, weak ankle dorsiflexion, depressed tendon reflexes, and high-arched feet.

It is important to establish a genetic cause of CMT hereditary neuropathy, as it can assist health providers in genetic counseling as well as discussions surrounding prognosis.

Bird TD. Charcot-Marie-Tooth (CMT) Hereditary Neuropathy Overview. 1998 Sep 28 [Updated 2025 Jan 23]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1358/

GeneReviews: Hereditary Neuropathy with Liability to Pressure Palsies

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.

Hereditary neuropathy with liability to pressure palsies (HNPP) should be suspected in individuals with the following clinical findings:

- Repeated acute focal sensory and motor neuropathies, mainly at entrapment sites
- Nerve palsy (without pain) after minor trauma or compression
- Focal weakness, atrophy, or sensory loss (which could indicate prior nerve palsy)
- Complete spontaneous recovery from neuropathies (in 50% of occurrences) within weeks

Affected individuals can be diagnosed with HNPP by identification of either the 1.5-megabase (Mb) recurrent deletion or another deletion involving *PMP22* (in 80%), or a pathogenic (or likely pathogenic) *PMP22* sequence variant (in 20%) via genetic testing.

Chrestian N. Hereditary Neuropathy with Liability to Pressure Palsies. 1998 Sep 28 [Updated 2020 Aug 27]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1392/

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Limb-Girdle Muscular Dystrophy Multigene Panel

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

In 2014, the American Academy of Neurology and the American Association of Neuromuscular and Electrodiagnostic Medicine issued evidenced-based guidelines for the diagnosis and treatment of limb-girdle and distal 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).

Narayanaswami P, Weiss M, Selcen D, et al. Evidence-based guideline summary: diagnosis and treatment of limb-girdle and distal dystrophies: report of the guideline development subcommittee of the American Academy of Neurology and the practice issues review panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology. 2014;83(16):1453-1463. doi:10.1212/WNL.0000000000000892

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.

Daras BT. Limb-girdle muscular dystrophy. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Updated February 2024. https://www.uptodate.com/contents/limb-girdle-muscular-dystrophy#H387926787

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***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).

The Myotonic Dystrophy Foundation. Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type I (Published in 2018). Available at: https://www.myotonic.org/sites/default/files/MDF_2018_CareConsiderationsDM1_2019_1_4.pdf

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 (page 22).

The Myotonic Dystrophy Foundation. Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type II (Published November 5, 2019). Available at: https://www.myotonic.org/sites/default/files/pages/files/Myotonic-ClinicalCareRecs-AdultsDM2-2019-11-05.pdf

American College of Medical Genetics and Genomics (ACMG)

In 2024, ACMG published revised technical standards and guidelines for myotonic dystrophy type 1. These standards discuss genetic testing for confirming a diagnosis in symptomatic individuals, including those with a less clear-cut clinical presentation, as well as predictive testing for patients without symptoms with an identified mutation within the family (p. 5).

Seifert BA, Reddi HV, Kang BE, et al. Myotonic dystrophy type 1 testing, 2024 revision: A technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2024;26(8):101145. doi:10.1016/j.gim.2024.101145

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)
    - leg myotonia, especially while climbing a staircase or trying to run fast
    - electrical myotonia (repetitive spontaneous discharges 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."

Schoser B. Myotonic Dystrophy Type 2. 2006 Sep 21 [Updated 2020 Mar 19]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1466/

Bird TD. Myotonic Dystrophy Type 1. 1999 Sep 17 [Updated 2024 Mar 21]. In: Adam MP, Everman DB, Mirzaa GM, et al, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1165/

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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.

Klein C, Lohmann K, Marras C, et al. Hereditary Dystonia Overview. 2003 Oct 28 [Updated 2017 Jun 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1155/

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Parkinson's Disease Multigene Panel

GeneReviews: Parkinson's Disease OverviewGeneReviews 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 the Monogenic Parkinson's Disease GeneReviews, establishing a specific genetic cause of Parkinson's 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's 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.

Morris H, Lim SY. Monogenic Parkinson Disease Overview. 2004 May 25 [Updated 2025 May 15]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle

(WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK1223/

Gasser et al

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 participating in innovative trials” (p. 777).

Gasser T. Genetic testing for Parkinsons disease in clinical practice. J Neural Transm. 2023; 130(6):777-782.

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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
- Impaired vibration sensation in the distal lower extremities

They suggest a multi-gene panel as the genetic testing strategy most likely to 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.

Hedera P. Hereditary Spastic Paraplegia Overview. 2000 Aug 15 [Updated 2021 Feb 11]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1509/

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Congenital Myasthenic Syndromes Multigene Panel

GeneReviews: Congenital Myasthenic Syndromes

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.

Abicht A, Müller JS, Lochmüller H. Congenital Myasthenic Syndromes Overview. 2003 May 9 [Updated 2021 Dec 23]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1168/

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CLCN1 Sequencing and/or Deletion/Duplication Analysis

Stunnenberg et al

In their 2020 practice resource titled “Guidelines on clinical presentation and management of nondystrophic myotonias,” an international group of experts, including US-based clinicians, include the following as signs of *CLCN1*-associated myotonia congenita (pp 5-6):

- Onset in the first decade of life

- Moderate worsening over time
- Myotonia (muscle stiffness), particularly of the legs, that may improve with moderate activity
- Muscle hypertrophy
- Percussion myotonia
- Transient paresis
- Absence of muscle wasting or systemic symptoms

The authors go on to propose a diagnostic algorithm, which includes testing for clinical and/or electrical myotonia followed by confirmatory genetic testing including *CLCN1* analysis (p. 7, p. 23).

Stunnenberg BC, LoRusso S, Arnold WD, et al. Guidelines on clinical presentation and management of nondystrophic myotonias. Muscle Nerve. 2020;62(4):430-444. doi:10.1002/mus.26887

GeneReviews: Myotonia Congenita

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).

Dunø M, Colding-Jørgensen E. Myotonia Congenita. 2005 Aug 3 [Updated 2021 Feb 25]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1355/

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.

Bryan ES, Alsaleem M. Myotonia Congenita. [Updated 2022 Aug 29]. In: StatPearls [Internet]. Treasure Island (FL): Statpearls Publishing; 2025 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562335/

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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.

The diagnosis of hypoPP (hypokalemic periodic paralysis) is established in a proband who meets the consensus diagnostic criteria for primary hypokalemic periodic paralysis:

- 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.

Weber F, Lehmann-Horn F. Hypokalemic Periodic Paralysis. 2002 Apr 30 [Updated 2018 Jul 26]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle

(WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1338/

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DEFINITIONS

1. **Autosomal dominant pattern of inheritance**[1] refers to a type of transmission of a genetic condition in which only one mutated copy of a gene (rather than two) is necessary for an individual to manifest the disease. These conditions 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.
2. **Childhood** is the period of development until the 18th birthday.
3. **Calf pseudohypertrophy** is defined as an enlarged (hypertrophic) appearance of the calf muscles due to replacement of the muscle with fat or connective tissue.
4. **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.
5. **Early-onset Alzheimer's disease** is defined as Alzheimer's disease occurring in an individual under age 65.
6. **Myotonia** is defined as impaired relaxation of skeletal muscle after voluntary contraction.
7. **Neonate** is a baby who is four weeks old or younger.
8. **Gower maneuver** is a particular way of moving from sitting to standing in individuals with severe proximal muscle weakness, especially in children with muscular dystrophy. The maneuver involves pulling up to hands and knees followed by "walking" the hands up the legs to push up into a standing position.

[1] 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.

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ADDITIONAL REFERENCES

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Note: The Health Plan uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

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