Revision log
Coding Implications

CONCERT GENETIC TESTING: NEUROLOGY

OVERVIEW

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

For additional information see the Rationale section.

POLICY REFERENCE TABLE

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2024, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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.

CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Comprehensive Neuromuscular Disorders Panel			
Comprehensive Neuromuscular Disorders Panel	Comprehensive Neuromuscular Panel (PreventionGenetics, part of	81161, 81404, 81405, 81406, 81479, G12, G13, G23-G26, G31, G32, G36,	23, 28, 32, 35

	Exact Sciences)	G37	
	Comprehensive Neuromuscular Disorders Panel (Invitae)		
	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	13
	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	8
	SMN1 Sequencing Analysis (Fulgent Genetics)		
	Genomic Unity *SMN1/2* Analysis - 0236U (Variantyx Inc.)		
SMN2 Deletion/Duplication Analysis	*SMN2* Deletion/Duplication (GeneDx)	81401, G12, Z84.81	

Rett Syndrome			
MECP2 Sequencing and/or Deletion/Duplication Analysis	*MECP2* Full Gene Sequencing and Deletion/Duplication (Invitae)	81302, 81304, 0234U, F70-F79, F80, F81, F82, F84, F88, F89, Z13.4, Z82.79, Z84	37
	MECP2 Gene Sequencing & Del/Dup (GeneDx)		
	Genomic Unity *MECP2* Analysis - 0234U (Variantyx, Inc.)		
Epilepsy			
Epilepsy Multigene Panel	Comprehensive Epilepsy Panel (Blueprint Genetics)	81185, 81189, 81302, 81406, 81419, 81479, G40.001- G40.919	33
	Comprehensive Epilepsy Panel (GeneDx)		
	Clinical Epilepsy NGS Panel (LabCorp)		
	EpilepsyNext (Ambry Genetics)		
	Epilepsy Panel (Invitae)		
Alzheimer's Disease			
PSEN1, PSEN2, and *APP* Sequencing and/or Deletion/Duplication Analysis	*PSEN1* Full Gene Sequencing and Deletion/Duplication (Invitae)	81405, 81406, 81479, F03, G30, G31.1, R41.0, R41.81, Z13.858, Z82.0, Z84.81	5, 6
	Alzheimer's Disease, Familial via the *PSEN2* Gene (PreventionGenetics, part of Exact Sciences)		

	APP Full Gene Sequencing and Deletion/Duplication (Invitae)		
	Alzheimer's Disease, Familial, Panel (PreventionGenetics, part of Exact Sciences)		
	Hereditary Alzheimer's Disease Panel (Invitae)		
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	2, 3
Amyotrophic Lateral Sclerosis (ALS)			
Targeted *C9orf72* Repeat Expansion Testing and Amyotrophic Lateral Sclerosis (ALS) Multigene Panels	Amyotrophic Lateral Sclerosis (ALS) Panel (PreventionGenetics, part of Exact Sciences)	81179, 81403, 81404, 81405, 81406, 81407, 81479, S3800, G12.21	11, 40
	Amyotrophic Lateral Sclerosis Panel (Invitae)		
Duchenne and Becker Muscular Dystrophy			
Diagnostic *DMD* Sequencing and/or Deletion/Duplication Analysis	Dystrophinopathies Test (Invitae)	81161, 81408, 0218U, G71.01, R62.59, Z84.81	12, 27
	Duchenne/Becker MD (DMD) Gene Sequencing (GeneDx)		
	Genomic Unity DMD Gene Analysis - 0218U (Variantyx)		
Facioscapulohumeral Muscular Dystrophy (FSHD)			

D4Z4 Haplotype Analysis, and/or *SMCHD1* and *DNMT3B* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	*FSHD1* Southern Blot Test (Quest Diagnostics)	81404, 81479, G71.02, Z84.81	1, 26
	Facioscapulohumeral Muscular Dystrophy 2 via the *SMCHD1* Gene (PreventionGenetics, part of Exact Sciences)		
	DNMT3B Full Gene Sequencing And Deletion/Duplication (Invitae)		
	FSHD-(FSHD1 & FSHD2) Detection of Abnormal Alleles with Interpretation (University of Iowa Hospitals and Clinics - Department of Pathology)		
Friedreich's Ataxia			
FXN Repeat Analysis and/or Sequencing Analysis	Friedreich Ataxia (*FXN*) Repeat Expansion Test (Athena Diagnostics)	81284, 81285, 81286, 81404, 0233U, G11, Z84.81	10, 13
	Friedreich Ataxia (*FXN*) DNA Sequencing Test (Athena Diagnostics)		
	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	9, 14, 38

Inherited Peripheral Neuropathy (Charcot-Marie-Tooth and Hereditary Neuropathy with Liability to Pressure Palsies)			
PMP22 Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	Deletion/Duplication (PMP22) (GeneDx)	81324, 81325, 81448, G60.0, G60.8, G60.9	4, 15
	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	7, 41
	Limb-Girdle Muscular Dystrophy Panel (Invitae)		
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	16, 17, 18, 19, 36
	Myotonic Dystrophy 2 (*ZNF9 / CNBP*) Genetic Testing (Repeat Expansion) (LabCorp)		
Hereditary Dystonia			
Hereditary Dystonia	Dystonia Panel (GeneDx)	81404, 81405, 81406,	20

Multigene Panel	Dystonia Panel (PreventionGenetics, part of Exact Sciences)	81407, 81408, 81479, G24.1, G24.9	
	Dystonia Comprehensive Panel (Invitae)		
Parkinson's Disease			
Parkinson's Disease Multigene Panel	Parkinson Disease Panel (Blueprint Genetics)	81479, G20	21, 34
	Parkinson Disease Panel (GeneDx)		
	Invitae Parkinson Disease and Parkinsonism Panel (Invitae)		
Hereditary Spastic Paraplegia			
Hereditary Spastic Paraplegia Multigene Panel	Spastic Paraplegia Panel (Blueprint Genetics)	81448, G11.4, G82.2	22
	Hereditary Spastic Paraplegia Comprehensive Panel (Invitae)		
Congenital Myasthenic Syndrome			
Congenital Myasthenic Syndromes Multigene Panel	Congenital Myasthenic Syndrome Panel (PreventionGenetics, part of Exact Sciences)	81406, 81407, 81479, G70.2	23
	Congenital Myasthenic Syndrome Panel (Invitae)		
Myotonia Congenita			

CLCN1 Sequencing and/or Deletion/Duplication Analysis	Myotonia Congenita via the *CLCN1* Gene (PreventionGenetics, part of Exact Sciences)	81406, 81479, G71.12	24, 39
	CLCN1 Full Gene Sequencing and Deletion/Duplication (Invitae)		
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)	81406, 81479, E87.6, G72.3	25
	SCN4A Full Gene Sequencing and/or Deletion/Duplication (Invitae)		
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	29, 30, 31

RELATED POLICIES

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

- ***Reproductive Testing: Prenatal Diagnosis*** for criteria related to fetal diagnostic testing for genetic disorders during pregnancy

- ***Reproductive Testing: Carrier Screening*** for criteria related to parental carrier screening for genetic disorders before or during pregnancy
- ***Specialty Testing: Toxicology and Pharmacogenetics*** for criteria related to drug and treatment response and toxicity testing
- ***Specialty Testing: Multisystem Genetic Conditions*** for 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 criteria related to preimplantation diagnosis
- ***General Approach to Laboratory Testing*** or 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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CRITERIA

It is the policy of health plans affiliated with Centene Corporation® that the specific genetic testing noted below is **medically necessary** when meeting the related 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/enrollee meets either of the following:

1. The member/enrollee 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/enrollee 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/enrollee meets one of the following:

1. The member/enrollee'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/enrollee underwent targeted or single-gene analysis for a neuromuscular disorder (e.g., *SMN1, DMD, PMP22*) and the results were non-diagnostic.

II. Current evidence does not support comprehensive neuromuscular panel analysis to establish a genetic diagnosis for a neuromuscular disorder 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/enrollee 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. Current evidence does not support comprehensive ataxia panel analysis to establish a genetic diagnosis of an ataxia 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/enrollee has a positive newborn screen for SMA, **OR**

   B. The member/enrollee 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. Current evidence does not support *SMN1* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of spinal muscular atrophy (SMA) 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/enrollee has a diagnosis of spinal muscular atrophy.

II. Current evidence does not support *SMN2* deletion/duplication analysis 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/enrollee 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/enrollee 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/enrollee 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. Current evidence does not support *MECP2* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of Rett syndrome 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/enrollee 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. Current evidence does not support the use of an epilepsy multigene panel for all other indications.

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ALZHEIMER 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/enrollee is 18 years of age or older, **AND**

B. The member/enrollee 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/enrollee 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. Current evidence does not support genetic testing for Alzheimer's disease via other genes.[2]

III. Current evidence does not support *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) 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 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/enrollee has a diagnosis of Alzheimer's disease, **AND**

B. The member/enrollee is being evaluated for suitability of treatment with monoclonal antibodies directed against aggregated forms of beta amyloid (such as Leqembi or Kisunla).

II. Current evidence does not support *APOE* variant analysis 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/enrollee 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. Current evidence does not support targeted *C9orf72* hexanucleotide repeat expansion testing and multigene panel analysis to establish a genetic etiology of amyotrophic lateral sclerosis (ALS) 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/enrollee has all of the following clinical characteristics of DMD:

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

2. Symptoms presenting before age five years, **AND**

3. Wheelchair dependency before age 13 years, **AND**

4. Elevated serum creatine kinase concentration, typically more than 10 times the normal levels, **OR**

B. The member/enrollee 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/enrollee 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/enrollee is an asymptomatic female, **AND**

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

II. Current evidence does not support *DMD* sequencing and/or deletion/duplication analysis to establish a diagnosis of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) 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/enrollee 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. Current evidence does not support 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 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/enrollee is symptomatic, **AND**

1. The member/enrollee 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/enrollee is asymptomatic[1], **AND**

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

II. Current evidence does not support *FXN* repeat analysis and/or sequencing analysis to establish or confirm a diagnosis of Friedreich's Ataxia 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/enrollee 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/enrollee has a clinical diagnosis of Huntington's disease, **OR**

C. The member/enrollee is undergoing predictive testing[1], **AND**

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

2. The member/enrollee is 18 years of age or older**, AND**

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

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

II. Current evidence does not support *HTT* repeat analysis to establish a diagnosis or for predictive testing of Huntington's disease (HD) 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/enrollee 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. Current evidence does not support *PMP22* sequencing and/or deletion/duplication analysis or multigene panel analysis to establish a genetic diagnosis of an inherited peripheral neuropathy 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/enrollee is symptomatic, **AND**

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

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

1. The member/enrollee has a close relative diagnosed with limb-girdle muscular dystrophy whose genetic status is unavailable.

II. Current evidence does not support multigene panel analysis to establish a diagnosis of limb-girdle muscular dystrophy 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/enrollee meets either of the following:

1. The member/enrollee 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/enrollee 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/enrollee is asymptomatic, **AND**
1. The member/enrollee is 18 years of age or older, **AND**
2. The member/enrollee has a first-degree relative with myotonic dystrophy type 1 or 2.

II. Current evidence does not support *DMPK* repeat analysis and *CNBP* repeat analysis to establish a diagnosis of myotonic dystrophy 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/enrollee has a clinical presentation consistent with dystonia or patterns of abnormal, repetitive, dystonic movements.

II. Current evidence does not support multigene panel analysis to establish a genetic diagnosis of hereditary dystonia 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/enrollee has a clinical diagnosis of Parkinson's disease, **AND**

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

II. Current evidence does not support multigene panel testing to establish a genetic diagnosis of Parkinson's disease 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/enrollee 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. Current evidence does not support multigene panel analysis to establish a genetic diagnosis of hereditary spastic paraplegia 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/enrollee 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. Current evidence does not support multigene panel analysis to establish a genetic diagnosis of congenital myasthenic syndromes 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/enrollee 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. Current evidence does not support *CLCN1* sequencing and/or deletion/duplication analysis to establish a genetic diagnosis of myotonia congenita 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 Periodic Paralysis Multigene Panel to establish a genetic diagnosis of periodic paralysis is considered **medically necessary** when:

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

   B. The member/enrollee has had two or more attacks of muscle weakness with documented serum potassium less than 3.5 mEq/L, **OR**

   C. The member/enrollee has had one attack of muscle weakness, **AND**

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

   D. The member/enrollee has three or more of the following features:

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

      2. Muscle weakness involving at least 1 limb lasting longer than two hours, **OR**

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

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

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

      6. Positive long exercise test.

II. Current evidence does not support *CACNA1S* and *SCN4A* sequencing and/or deletion/duplication analysis, or Periodic Paralysis Multigene Panel to establish a genetic diagnosis of periodic paralysis 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/enrollee demonstrates clinical features consistent with the disorder (the list is not meant to be comprehensive, see II below):

   A. AADC deficiency

   B. Hereditary Transthyretin Amyloidosis

   C. X-linked Adrenoleukodystrophy

   D. L1 Syndrome

   E. SCN9A Neuropathic Pain Syndromes

   F. Cerebral Cavernous Malformation, Familial

   G. STAC3 Disorder.

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

Comprehensive Neuromuscular Disorders Panel

American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM)

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

Winder et al.

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

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).

GeneReviews: Congenital Myasthenic Syndromes Overview

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

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

Neonatal presentation:

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

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

- 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.

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Comprehensive Ataxia Panel

Jayadev et al

An overview of hereditary ataxias (2013, p. 673) stated the following in regard to “establishing the diagnosis of hereditary ataxia:

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

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

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).

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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.

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SMN2 Deletion/Duplication Analysis

GeneReviews: Spinal Muscular Atrophy

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    - 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.

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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.

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Epilepsy Multigene Panel

National Society of Genetic Counselors

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

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

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

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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)

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

- Pediatric testing for AD should not occur.
- Prenatal testing for AD is not advised if the patient intends to continue a pregnancy with a mutation.
- Testing for genes associated with early-onset autosomal dominant AD should be offered in the following situations:
    - A symptomatic individual with EOAD [early-onset Alzheimer's disease] in the setting of a family history of dementia or the setting of an unknown family history (eg, adoption).
    - Autosomal dominant family history of dementia with one or more cases of EOAD.
    - A relative with a mutation consistent with EOAD (currently *PSEN1/2* or *APP*) (p. 601).

Alzheimer's disease 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), he/she should be counseled according to the recommended protocol (p. 601).

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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 Kisluna, 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).

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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).

GeneReviews: Amyotrophic Lateral Sclerosis Overview

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

The recommendations for genetic testing for Amyotrophic Lateral Sclerosis are as follows:

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

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

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

- Together with the absence of both of the following:
    - Electrophysiologic or pathologic evidence of other disease processes that could explain the signs of LMN and/or UMN degeneration
    - Neuroimaging evidence of other disease processes that could explain the observed clinical and electrophysiologic signs

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

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

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

DMD Care Considerations Working Group

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

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

diagnosis of DMD, then a muscle biopsy sample should be tested for the presence of dystrophin protein by immunohistochemistry of tissue cryosections or by western blot of a muscle protein extract" (p. 254).

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.

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

Duchenne muscular dystrophy (DMD)

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

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

Becker muscular dystrophy (BMD):

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

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

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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 2021) on FSHD state that genetic testing can confirm the diagnosis in many patients with FSHD type 1 and further state that if the patient tests negative for the D4Z4 contraction, testing for FSHD type 2 or other myopathies can be 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).

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.

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FXN Repeat Analysis and/or Sequencing Analysis

American College of Medical Genetics

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

"Establishing the diagnosis of hereditary ataxia requires:

- Detection on neurological examination of typical clinical signs including poorly coordinated gait and finger/hand movements, dysarthria (incoordination of speech), and eye movement abnormalities such as nystagmus, abnormal saccade movements, and ophthalmoplegia.
- Exclusion of nongenetic causes of ataxia.
- Documentation of the hereditary nature of the disease by finding a positive family history of ataxia, identifying an ataxia-causing 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)

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, typically with onset before age 25 years.[2]
    - Progressive ataxia of gait and limbs
    - Dysarthria
    - Decrease in/loss of position sense and/or vibration sense in lower limbs ∘
    - Pyramidal weakness of the legs, extensor plantar responses
- Musculoskeletal features
    - Muscle weakness
    - Scoliosis

    - Pes cavus
- Hypertrophic non-obstructive cardiomyopathy
- Endocrinologic features
    - Glucose intolerance
    - Diabetes mellitus
- Optic atrophy and/or deafness
- Family history consistent with autosomal recessive inheritance Note: Absence of a family history of autosomal recessive inheritance does not preclude the diagnosis.

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

[2]In atypical cases, onset may be delayed.

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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.

Huntington's Disease Society of America (HDSA)

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

National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC) issued a statement in 2018 which encourages deferring predictive genetic testing of minors for adult-onset conditions when results will not impact childhood medical management or significantly benefit the child. Predictive testing should optimally be deferred until the individual has the capacity to weigh the associated risks, benefits, and limitations of this information, taking his/her circumstances, preferences, and beliefs into account to preserve his/her autonomy and right to an open future.

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

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

GeneReviews: Charcot-Marie-Tooth Hereditary Neuropathy Overview

Individuals with CMT [Charcot-Marie-Tooth] manifest symmetric, slowly progressive distal motor neuropathy of the arms and legs usually beginning in the first to third decade and resulting in weakness and atrophy of the muscles in the feet and/or hands. The affected individual typically has distal muscle weakness and atrophy, weak ankle dorsiflexion, depressed tendon reflexes, and *pes cavus* foot deformity (i.e., high-arched feet).

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

GeneReviews: Hereditary Neuropathy with Liability to Pressure Palsies

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

Typical clinical findings:

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

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

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Limb-Girdle Muscular Dystrophy Multigene Panel

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

The American Academy of Neurology and the American Association of Neuromuscular and Electrodiagnostic Medicine (2014) issued evidenced-based guidelines for the diagnosis and treatment of limb-girdle and distal dystrophies. These guidelines included a systematic review, which identified common features of limb-girdle muscular dystrophy (LGMD) including slowly progressive symmetrical weakness. The age of onset is highly variable but usually adolescence to early adulthood.

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

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

UpToDate: Limb-girdle Muscular Dystrophy

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

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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).

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).

American College of Medical Genetics

ACMG published technical standards and guidelines for myotonic dystrophy type 1 in 2009 and reaffirmed in 2015. In it, they state: "Indications for genetic testing: This test is often used for

symptomatic confirmatory diagnostic testing and predictive testing, after the identification of the mutation in an affected family member" (p. 553).

GeneReviews-Myotonic Dystrophy Type 1 and Myotonic Dystrophy Type 2

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

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

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

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

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

DM2 should be suspected in individuals with the following findings:

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

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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.

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Parkinson's Disease Multigene Panel

GeneReviews - Parkinson's Disease 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.

Per the 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.

Gasser et al (2023)

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

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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.

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Congenital Myasthenic Syndromes Multigene Panel

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

GeneReviews 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.

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CLCN1 Sequencing and/or Deletion/Duplication Analysis

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).

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.

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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.

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DEFINITIONS

1. **Autosomal dominant** inheritance patterns[1] 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. **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.
4. **Early-onset Alzheimer's disease** is defined as Alzheimer's disease occurring in an individual under age 65.
5. **Myotonia** is defined as impaired relaxation of skeletal muscle after voluntary contraction.
6. A **neonate** is a baby who is four weeks old or younger.

[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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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	03/23	03/23
Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Overview: added "establish or"; removed "the disease, but conventional diagnostic methods…" and added "genetic disorder, for whom clinical evidence…"; removed "the" and replaced with "a genetic"; removed "alter some aspects" and replaced with "inform clinical"; removed "may" and replaced with "/or"; added "epilepsy". For Policy Reference Table: changed "Neuromuscular NGS Panel…" to "Comprehensive Neuromuscular Disorders Panel"; added "Rett Syndrome"; added "MECP2 Sequencing…"; changed "Childhood Onset Epilepsy Panel…" to "Comprehensive Epilepsy Panel…"; added "CADASIL"; added "NOTCH3…"; changed "TREM2, and other	10/23	10/23

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Variant Analysis" to "Variant Analysis for Alzheimer's Disease"; changed "DMD Deletion/Duplication Analysis" to "DMD Full Gene Sequencing…" and "Duchenne/Becker MD…"; changed "DMPK Repeat Analysis" to "Myotonic Dystrophy…". For Comprehensive Neuromuscular Disorders Panel: under I.A. removed "clinical features of a" and replaced with "at least one of the following"; added I.A.1. "Neonatal respiratory…"; added I.A.2. "Neonatal joint contractures…"; added I.A.3. "Stridor, feeding difficulties…"; added I.A.4. "Abnormal muscle…"; added I.A.5. "Abnormal muscle…"; added I.A.6. "Eyelid ptosis…"; added I.A.7. "Facial and bulbar…"; added I.A.8. "Spinal deformity…"; added I.A.9. "Abnormal electromyography…"; in I.B.1. removed "member/enrollee" and replaced with "member/enrollee's presentation"; removed "highly suspected…" and replaced with "consistent with a"; added "targeted or"; removed "would be more" and replaced with "is"; under I.B.2. removed "previously underwent" and replaced with "underwent targeted"; removed "did not definitively" and replaced with "were non-diagnostic". For Comprehensive Ataxia Panel: removed "clinical features of spinocerebellar ataxia". For Spinal Muscular Atrophy: removed "clinical features of SMA". Added "Rett Syndrome" panel. Added "CADASIL" panel. For Alzheimer's Disease Panel: removed "or Multigene Panel"; under I. removed "or multigene panel…"; under I.B.1. removed "The member/enrollee has a close relative…" and replaced with "Has a family history of dementia…"; under I.B.1.a. added "Has at least one relative…"; under I.C.1. removed "Has a diagnosis of dementia…" and replaced with "Was diagnosed with dementia"; under I.C.2. removed "Has a diagnosis" and replaced with "Was diagnosed with"; removed "One or more close relatives…" and added "that is consistent with an autosomal dominant pattern…"; added I.C.2.b. "Has at least one close relative…"; added II. "Genetic testing for Alzheimer's…". For APOE Variant Analysis for Alzheimer's Disease Panel: added "APOE variant analysis" and removed "or TREM2…"; removed statement "*Predictive testing…" and added "is considered medically necessary…"; added I.A. "The member/enrollee is being evaluated…"; added II. "APOE variant analysis…". For Amyotrophic Lateral Sclerosis (ALS) Panel: Changed title from "Familial Amyotrophic Lateral Sclerosis (FALS) Multigene Panel" to "Amyotrophic Lateral Sclerosis (ALS) Multigene Panel; and removed "familial" throughout the panel wording; removed "clinical features of ALS:"; and removed "FALS" and replaced with "ALS". For Duchenne and Becker Muscular Dystrophy Panel: removed I.A. "The member/enrollee is a male, AND"; replaced "findings" with "characteristics"; under I.A.2. replaced "For BMD, the member/enrollee meets the following" with "The following clinical characteristics of BMD"; under I.A.2.b. replaced "Any" with "At least one"; for I.A.2.B. added "(male or female)"; for I.A.2.B.1. removed "and/or molecular"; for I.A.2.C. replaced "a" with "an asymptomatic". For Facioscapulohumeral Muscular Dystrophy (FSHD) Panel: under I.A. removed "clinical features of FSHD:"; under I.A.3. removed "FSHD with" and "AND" and removed "The member/enrollee does not have a first		

Reviews, Revisions, and Approvals	Revision Date	Approval Date
degree relative…". For Friedreich's Ataxia Panel: under I.A.1. replaced "The member/enrollee has: with "Has" and removed "diagnosed"; under I.B. replaced "meets both" with "has at least two"; under I.B.1. replaced "The member/enrollee has been diagnosed…" with "Progressive ataxia…"; added I.B.2. "Dysarthria"; added I.B.3. "Decrease in/loss of position…"; added I.B.4. "Pyramidal weakness…"; added. I.B.5. "Extensor plantar…"; added. I.B.6. "Muscle weakness…"; added I.B.7. "Scoliosis, OR"; added I.B.8. "Pes cavus…"; added I.B.9. "Hypertrophic…"; added I.B.10. "Glucose intolerance…"; added I.B.11. "Optic atrophy…". For Huntington's Disease Panel: under I.A. removed "Progressive" and replaced with "clinical features of Huntington's Disease…"; removed I.A.1. "Cognitive decline…"; removed I.A.2. "Changes in personality…"; removed I.A.3. "Depression…"; in I.A.B. removed "Family history…" and added "The member/enrollee has a clinical diagnosis…". For Inherited Peripheral Neuropathies Panel: under I.A. removed "does not have a clinical diagnosis…" and replaced with "displays one or more of the following"; in I.B. removed "The" and replaced with "If a panel is ordered…". For Myotonic Dystrophy Panel: in I.A. added "is symptomatic and"; in I.A.2. removed "clinical features…". For Hereditary Dystonia Panel: under I.A. removed "all of the following…" and added "clinical presentation consistent with…". For Parkinson Disease, Parkinson Disease Multigene Panel: changed name from LRRK2 Sequencing and/or Deletion/Duplication Analysis…" to "Parkinson Disease Multigene Panel"; in I. added "Multigene"; in I.B. added "The member/enrollee has a"; removed I.C. "The panel includes…"; in II. added "Multigene". For Hereditary Spastic Paraplegia Multigene Panel: in I.A.4. removed "AND…". For Congenital Myasthenic Syndromes Multigene Panel: under I.A. removed "a history…"; added "1. Neonatal respiratory insufficiency…"; added "2. Neonatal joint contractures…"; added "3. Stridor…"; added "4. Abnormal muscle fatigability/weakness…"; added "5. Delayed motor milestones…;"; added "6. Eyelid ptosis…"; added "7. Facial…"; added "8. Spinal deformity…"; added "9. Abnormal electromyography…". For CLCN1 Sequencing and/or Deletion/Duplication Analysis Panel: under I.A. replaced "episodes" with "any of the following"; in I.A.1. added "Episodes" and replaced "AND" with "OR"; in I.B. removed "AND"; in I.B.2. removed "Serum creatine kinase…" and added "OR"; removed statement Myotonia is defined…". For CACNA1S and SCN4A Sequencing and/or Deletion/Duplication Analysis, added to the title "or Periodic Paralysis Multigene Panel"; in I. and II. added "or Periodic Paralysis Multigene Panel". For Other Covered Epilepsy, Neuromuscular, and Neurodegenerative Disorders Panel: under I. added "A. AADC deficiency"; under II. added "and Molecular". For Notes/And Definitions: added "7. Myotonia…", "8. Autosomal dominant…"; added statement "*Factors such as…". For Background and Rationale: replaced "inheritance patterns" to "genetic testing"; added "GeneReviews: Congenital Myasthenic Syndromes Overview…"; added "Rett Syndrome – MECP2 Sequencing…"; added "CADASIL-NOTCH3		

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Sequencing…"; removed "Disease- APOE…"; added "Alzheimer Disease…"; For Facioscapulohumeral Muscular Dystrophy (FSHD) - *FSHD1* Deletion/Duplication or Haplotype Analysis and/or *SMCHD1* and *DNMT3B* Sequencing and/or Deletion Analysis or Multigene Panel: removed "and no first degree relative…". For Huntington's Disease- HTT Repeat Analysis: replaced "National Society…" with "Huntington's Disease…"; added "The Huntington's Disease Society of America…". For Inherited Peripheral Neuropathy (Charcot-Marie-Tooth and Hereditary Neuropathy with Liability to Pressure Palsies) - *PMP22* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel: added "'Establishing a specific genetic cause…'"; added "'The diagnosis of HNPP…'". For Limb Girdle Muscular Dystrophy Multigene Panel**:** removed "(presenting at highly variable ages.)" and added "The age of onset…". For *DMPK* and/or *CNBP* (ZNF9) Repeat Analysis Panel: replaced "2021" with "2009 and reaffirmed in 2015"; removed "The test is also useful…". For Parkinson Disease - *LRRK2* Sequencing and/or Deletion/Duplication Analysis and Parkinson Disease Multigene Panel: removed "Usefulness of Genetic Testing…"; added "Genetic testing for Parkinson's Disease…"; removed "in Parkinson Disease…"; added "offered for PD…". For Myotonia Congenita - *CLCN1* Sequencing and/or Deletion/Duplication Analysis: added "Per GeneReviews…"; removed "Serum creatine kinase…"; added "Myotonia Congenita…"; removed "Electromyography performed with needle…" and added "Electromyography is a useful tool…".		
Semi-annual review. Updated title to reflect V2.2024 version. In Known Familial Variant Analysis for Epilepsy, Neurodegenerative, and Neuromuscular disorders criteria, moved criteria to policy "Genetic Testing: General Approach to Genetic and Molecular Testing" to consolidate criteria for known familial variant tests. In *HTT* Repeat Analysis criteria, added age restriction for testing (18 or older). In Amyotrophic Lateral Sclerosis (ALS) Multigene Panel criteria, removed age restriction for testing (18 or older) given there are childhood onset forms of ALS. In *PMP22* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel criteria, removed minimum gene list; at present there is limited rationale for inclusion. In *PSEN1, PSEN2,* and *APP* Sequencing and/or Deletion/Duplication Analysis criteria, Clarified age requirement for symptomatic individuals diagnosed at or over age 66 (previous criteria stated "any age"). Minor rewording for clarity throughout. Coding, reference-table, background and references updated.	04/24	04/24
Semi-annual review. Updated title to reflect V1.2025. CLCN1 Sequencing and/or Deletion/Duplication Analysis: Updated GeneReviews copyright dates in Reference list. FXN Repeat Analysis and/or Sequencing Analysis: Specified that the member must be symptomatic to meet criteria in section A. Comprehensive Neuromuscular Disorders Panel: Added the following criteria in section 2,	11/24	11/24

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"Elevated serum creatine kinase levels"; Added the following language in the Background and Rationale, "The authors also recommend that "...genetic testing can also be considered in certain patients with asymptomatic CK [creatine kinase] elevations." (p. 261)"; Reformatting of criteria for ease of use. Congenital Myasthenic Multigene Panel: Updated GeneReviews copyright dates in Reference list. APOE Variant Analysis for Alzheimer's Disease: Updated language from, "The member is being evaluated for treatment with monoclonal antibodies..." to, "The member is being evaluated for suitability of treatment with monoclonal antibodies;" Added criterion for diagnosis of Alzheimer's disease; Added Kisluna as an additional example of treatment often guided by this testing. APOE Variant Analysis for Alzheimer's Disease: Updated test names in Policy Reference Table; Updated GeneReviews copyright dates in Reference list. D4Z4 Haplotype Analysis, and/or SMCHD1 and DNMT3B Sequencing and/or Deletion/Duplication Analysis or Multigene Panel: Removed test from Policy Reference Table; Updated GeneReviews copyright dates in Reference list and AAN reference reaffirmation date. DMD Sequencing and/or Deletion/Duplication Analysis: Updated criteria name to Diagnostic DMD Sequencing and/or Deletion/Duplication Analysis to differentiate between prenatal and post-natal versions of this criteria; Updated example test name in Policy Reference Table. SMN1 Sequencing and/or Deletion/Duplication Analysis: Updated criterion to the following language; "Muscle weakness, especially proximal muscles" from "Proximal to distal muscle weakness". Limb-girdle Muscular Dystrophy Multigene Panel: Made minor grammar changes in Background and Rationale. PSEN1, PSEN2, and APP Sequencing and/or Deletion/Duplication Analysis: Added the parenthetical "(Diagnosed under 65 years)" in areas of the policy referring to early onset Alzheimers disease in order to allow for more rapid medical review; Added "of age" to criteria I.C.2 to be consistent with other sections of the criteria. NOTCH3 Sequencing and/or Deletion/Duplication Analysis: Updated GeneReviews copyright dates in Reference list. Epilepsy Multigene Panel: Updated example tests in Policy Reference Table. Updated example tests in Policy Reference Table. CACNA1S and SCN4A Sequencing and/or Deletion/Duplication Analysis, or Periodic Paralysis Multigene Panel: Updated GeneReviews copyright dates in Reference list. Hereditary Dystonia Multigene Panel: Updated GeneReviews copyright dates in Reference list. MECP2 Sequencing and/or Deletion/Duplication Analysis: Removed outdated ACMG reference from Background and Rationale and References; Updated GeneReviews copyright dates in Reference list. Parkinson Disease Multigene Panel: Removed reference (Cook, et al) from Background and Rationale and References; Updated GeneReviews copyright dates in Reference list. Huntington Disease - HTT Repeat Analysis: Updated GeneReviews copyright dates in Reference list. Other Covered Epilepsy, Neuromuscular, and Neurodegenerative Disorders: Updated GeneReviews copyright dates in Reference list. Hereditary Spastic Paraplegia Multigene Panel: Updated example		

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test in Policy Reference Table; Updated GeneReviews copyright dates in Reference list. Myotonic Dystrophy - DMPK and/or CNBP (ZNF9) Repeat Analysis: Updated GeneReviews copyright dates in Reference list.		
Annual review. Policy name changed from Concert Genetic Testing: Epilepsy, Neurodegenerative, and Neuromuscular Conditions to Concert Genetic Testing: Neurology. Removed criteria for NOTCH3 Sequencing and/or Deletion/Duplication Analysis. Limb-Girdle Muscular Dystrophy Multigene Panel criteria: Added "The member is symptomatic" to criterion A and changed the indenting for the corresponding criterion for clarification and structural consistency. “Investigational” policy statements changed to state “current evidence does not support…” References, rationale and coding updated.	11/25	12/25

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering

benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, member/enrollees, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, member/enrollees and their representatives agree to be bound by such terms and conditions by providing services to member/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.