BSC_CON_2.14	Genetic Testing: Epilepsy, Neurodegenerative, and Neuromuscular Disorders		
Original Policy Date:	June 1, 2024	**Effective Date:**	June 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 51

Example Test Table

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

Policy Statements	Example Tests; Labs	Common CPT Codes
Comprehensive Neuromuscular Disorders Panel		
Comprehensive Neuromuscular Disorders Panel	Comprehensive Neuromuscular Panel (PreventionGenetics, part of Exact Sciences)	81161, 81404, 81405, 81406, 81479
	Comprehensive Neuromuscular Disorders Panel (Invitae)	
	Neuromuscular Disorders Panel (GeneDx)	
Comprehensive Ataxia Panel		
Comprehensive Ataxia Panel	Genomic Unity Ataxia Repeat Expansion Analysis (Variantyx, Inc.)	0216U
	Genomic Unity Comprehensive Ataxia Analysis (Variantyx, Inc.)	0217U
	Ataxia Xpanded Panel (GeneDx)	81185, 81189, 81286, 81403, 81404, 81479
	Ataxia Panel (Blueprint Genetics)	
Spinal Muscular Atrophy		
SMN1 Sequencing and/or Deletion/Duplication Analysis	SMN1 Diagnostic Testing (by MLPA) (PerkinElmer Genomics)	81329, 81401
	SMN1 Sequencing Analysis (Fulgent Genetics)	81336, 81405
	Genomic Unity SMN1/2 Analysis (Variantyx Inc.)	0236U
SMN2 Deletion/Duplication Analysis	SMN2 Deletion/Duplication (GeneDx)	81401
Rett Syndrome		
MECP2 Sequencing and/or Deletion/Duplication Analysis	MECP2 Full Gene Sequencing and Deletion/Duplication (Invitae)	81302, 81304
	MECP2 Gene Sequencing & Del/Dup (GeneDx)	
	Genomic Unity MECP2 Analysis (Variantyx, Inc.)	0234U
Epilepsy		
Epilepsy Multigene Panel	Comprehensive Epilepsy Panel (Blueprint Genetics)	81185, 81189, 81302, 81406, 81419, 81479

Policy Statements	Example Tests; Labs	Common CPT Codes
	Comprehensive Epilepsy Panel (GeneDx)	
	Infantile Epilepsy Panel (GeneDx)	
	Childhood-Onset Epilepsy Panel (GeneDx)	
	Invitae Epilepsy Panel (Invitae)	
CADASIL		
NOTCH3 Sequencing and/or Deletion/Duplication Analysis	NOTCH3 Full Gene Sequencing and Deletion/Duplication (Invitae)	81406, 81479
Alzheimer Disease		
PSEN1, *PSEN2*, and *APP* Sequencing and/or Deletion/Duplication Analysis	PSEN1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81405, 81479
	Alzheimer's Disease, Familial via the PSEN2 Gene (PreventionGenetics, part of Exact Sciences)	81406, 81479
	APP Full Gene Sequencing and Deletion/Duplication (Invitae)	81406, 81479
	Alzheimer's Disease, Familial, Panel (PreventionGenetics, part of Exact Sciences)	81405, 81406, 81479
	Hereditary Alzheimer's Disease Panel (Invitae)	
APOE Variant Analysis for Alzheimer's Disease	APOE Single Gene Test (Blueprint Genetics)	81401, 81479, S3852
Amyotrophic Lateral Sclerosis (ALS)		
Amyotrophic Lateral Sclerosis (ALS) Multigene Panel	Amyotrophic Lateral Sclerosis (ALS) Panel (PreventionGenetics, part of Exact Sciences)	81179, 81403, 81404, 81405, 81406, 81407, 81479, S3800
	Amyotrophic Lateral Sclerosis Panel (Invitae)	
Duchenne and Becker Muscular Dystrophy		
DMD Sequencing and/or Deletion/Duplication Analysis	DMD Full Gene Sequencing and Deletion/Duplication (Invitae)	81161
	Duchenne/Becker MD (DMD) Gene Sequencing (GeneDx)	81408
	Genomic Unity DMD Gene Analysis (Variantyx)	0218U
Facioscapulohumeral Muscular Dystrophy (FSHD)		
D4Z4 Haplotype Analysis, and/or *SMCHD1* and *DNMT3B* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	FSHD1 Southern Blot Test (Quest Diagnostics)	81404
	FSHD-(FSHD1 & FSHD2) Detection of Abnormal Alleles with Interpretation - 4qA/4qB Haplotyping (University of Iowa Hospitals and Clinics - Department of Pathology)	81404
	Facioscapulohumeral Muscular Dystrophy 2 via the SMCHD1 Gene (PreventionGenetics, part of Exact Sciences)	81479
	DNMT3B Full Gene Sequencing And Deletion/Duplication (Invitae)	
	FSHD-(FSHD1 & FSHD2) Detection of Abnormal Alleles with Interpretation (University of Iowa Hospitals and Clinics - Department of Pathology)	81404, 81479

Policy Statements	Example Tests; Labs	Common CPT Codes
Friedreich's Ataxia		
FXN Repeat Analysis and/or Sequencing Analysis	Friedreich Ataxia (FXN) Repeat Expansion Test (Athena Diagnostics)	81284, 81285
	Friedreich Ataxia (FXN) DNA Sequencing Test (Athena Diagnostics)	81286, 81404
	Genomic Unity FXN Analysis (Variantyx Inc)	0233U
Huntington's Disease (HD)		
HTT Repeat Analysis	Huntington Disease (HTT) Genetic Testing (Repeat Expansion) (LabCorp)	81271, 81274
Inherited Peripheral Neuropathy (Charcot-Marie-Tooth and Hereditary Neuropathy with Liability to Pressure Palsies)		
PMP22 Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	PMP22 Del/Dup Analysis (GeneDx)	81324
	PMP22 Gene Sequencing (GeneDx)	81325
	Charcot-Marie Tooth (CMT) - Comprehensive Panel (PreventionGenetics, part of Exact Sciences)	81448
	Charcot-Marie-Tooth Panel (GeneDx)	
Limb-Girdle Muscular Dystrophies (LGMD)		
Limb Girdle Muscular Dystrophy Multigene Panel	Limb-Girdle Muscular Dystrophy Panel (GeneDx)	81405, 81406, 81408, 81479
	Limb-Girdle Muscular Dystrophy Panel (Invitae)	
Myotonic Dystrophy		
DMPK and/or *CNBP* (ZNF9) Repeat Analysis	Myotonic Dystrophy 1 (DMPK) Genetic Testing (Repeat Expansion) (LabCorp)	81234, 81239, 81401, 81404, S3853
	Myotonic Dystrophy 2 (ZNF9 / CNBP) Genetic Testing (Repeat Expansion) (LabCorp)	81187, S3853
Hereditary Dystonia		
Hereditary Dystonia Multigene Panel	Dystonia Panel (GeneDx)	81404, 81405, 81406, 81407, 81408, 81479
	Dystonia Panel (PreventionGenetics, part of Exact Sciences)	
	Dystonia Comprehensive Panel (Invitae)	
Parkinson Disease		
Parkinson Disease Multigene Panel	Parkinson Disease Panel (BluePrint Genetics)	81479
	Parkinson Disease Panel (GeneDx)	
	Invitae Parkinson Disease and Parkinsonism Panel (Invitae)	
Hereditary Spastic Paraplegia		
Hereditary Spastic Paraplegia Multigene Panel	Comprehensive Hereditary Spastic Paraplegia Panel (GeneDx)	81448
	Hereditary Spastic Paraplegia Comprehensive Panel (Invitae)	
Congenital Myasthenic Syndrome		

Policy Statements	Example Tests; Labs	Common CPT Codes
Congenital Myasthenic Syndromes Multigene Panel	Congenital Myasthenic Syndrome Panel (PreventionGenetics, part of Exact Sciences)	81406, 81407, 81479
	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
	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
	SCN4A Full Gene Sequencing and/or Deletion/Duplication (Invitae)	
Other Covered Epilepsy, Neurodegenerative, and Neuromuscular Disorders		
Other Covered Epilepsy, Neuromuscular, and Neurodegenerative Disorders	See list below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479

Policy Statement

Comprehensive Neuromuscular Disorders Panel

I. Comprehensive neuromuscular panel analysis to establish a genetic diagnosis for a neuromuscular disorder (81161, 81404, 81405, 81406, 81479) may be considered **medically necessary** when **both** of the following are met:
   A. The member displays at least **one** of the following:
      1. Neonatal respiratory insufficiency, with sudden episodic apnea and cyanosis
      2. Neonatal joint contractures (e.g., arthrogryposis multiplex congenita)
      3. Stridor, feeding difficulties, poor suck/cry, choking spells, eyelid ptosis, or facial, bulbar, or generalized weakness in neonates
      4. Abnormal muscle fatigability/weakness
      5. Delayed motor milestones
      6. Eyelid ptosis or extraocular muscle weakness
      7. Facial and bulbar weakness with nasal speech and difficulties in coughing and swallowing
      8. Spinal deformity or muscle atrophy,
      9. Abnormal electromyography (EMG) testing showing a defect in neuromuscular transmission
   B. **One** of the following:
      1. The member's presentation is not consistent with a neuromuscular disorder for which targeted or single-gene analysis (e.g., *SMN1, DMD, PMP22*) is appropriate
      2. The member underwent targeted or single-gene analysis for a neuromuscular disorder (e.g., *SMN1, DMD, PMP22*) and the results were non-diagnostic.

II. Comprehensive neuromuscular panel analysis to establish a genetic diagnosis for a neuromuscular disorder (81161, 81404, 81405, 81406, 81479) is considered **investigational** for all other indications.

Comprehensive Ataxia Panel

III. Comprehensive ataxia panel analysis to establish a genetic diagnosis of an ataxia (81185, 81189, 81286, 81403, 81404, 81479, 0216U, 0217U) may be considered **medically necessary** when **both** of the following are met:
   A. The member displays **one or more** of the following:
      1. Poorly coordinated gait and finger/hand movements
      2. Weakness of the eye muscles (ophthalmoplegia)
      3. Dysarthria
      4. Eye movement abnormalities (nystagmus, abnormal saccade movements)
   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).

IV. Comprehensive ataxia panel analysis to establish a genetic diagnosis of an ataxia (81185, 81189, 81286, 81403, 81404, 81479, 0216U, 0217U) is considered **investigational** for all other indications.

Spinal Muscular Atrophy

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

V. *SMN1* sequencing and/or deletion/duplication analysis (81329, 81336, 81401, 81405, 0236U) to establish or confirm a diagnosis of spinal muscular atrophy may be considered **medically necessary** when **either** of the following are met:
   A. The member has a positive newborn screen for SMA
   B. The member has **any** of the following:
      1. History of motor difficulties, especially with loss of skills
      2. Proximal to distal muscle weakness
      3. Hypotonia
      4. Areflexia/hyporeflexia
      5. Tongue fasciculations
      6. Hand tremor
      7. Recurrent lower respiratory tract infections or severe bronchiolitis in the first few months of life
      8. Evidence of motor unit disease on electromyogram.

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

***SMN2* Deletion/Duplication Analysis**

VII. *SMN2* deletion/duplication analysis (81401) may be considered **medically necessary** when:
   A. The member has a diagnosis of spinal muscular atrophy.

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

Rett Syndrome

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

IX. *MECP2* sequencing and/or deletion/duplication analysis (81302, 81304, 0234U) to establish or confirm a diagnosis of Rett syndrome may be considered **medically necessary** when **all** of the following are met:
   A. The member experienced a period of developmental regression (range: ages 1-4 years) followed by recovery or stabilization (range: ages 2-10 years)
   B. The member has at least **one** of the following:

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

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

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

Epilepsy

Epilepsy Multigene Panel

XI. The use of an epilepsy multigene panel (81185, 81189, 81302, 81406, 81419, 81479) may be considered **medically necessary** when:
A. The member has a history of unexplained epilepsy (i.e., seizures not caused by acquired etiology such as trauma, infection, structural brain abnormality, and/or stroke).

XII. The use of an epilepsy multigene panel (81185, 81189, 81302, 81406, 81419, 81479) is considered **investigational** for all other indications.

CADASIL

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

XIII. *NOTCH3* sequencing and/or deletion/duplication analysis (81406, 81479) to establish or confirm a diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) may be considered **medically necessary** when **any** of the following are met:
A. The member has a family history of stroke and/or vascular dementia consistent with an autosomal dominant pattern of inheritance, **OR**
B. The member has at least **one** of the following clinical features of CADASIL:
1. Transient ischemic attacks and ischemic stroke
2. Cognitive impairment, manifesting initially with executive dysfunction, with a concurrent stepwise deterioration due to recurrent strokes to vascular dementia
3. Migraine with aura (mean age of onset of 30 years)
4. Psychiatric disturbances, most frequently mood disturbances and apathy

C. The member has at least **one** of the following brain imaging findings of CADASIL:
1. Symmetric and progressive white matter hyperintensities, often involving the anterior temporal lobes and external capsules
2. Lacunes of presumed vascular origin
3. Recent subcortical infarcts
4. Dilated perivascular spaces, sometimes referred to as subcortical lacunar lesions
5. Brain atrophy
6. Cerebral microbleeds.

XIV. *NOTCH3* sequencing and/or deletion/duplication analysis (81406, 81479) to establish or confirm a diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is considered **investigational** for all other indications.

Alzheimer Disease

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

XV. *PSEN1* (81405, 81479), *PSEN2* (81406, 81479), and/or *APP* (81406, 81479) sequencing and/or deletion/duplication analysis to establish a diagnosis or determine future risk to develop early-onset Alzheimer disease may be considered **medically necessary** when:
- A. The member is 18 years of age or older, **AND**
- B. The member is asymptomatic*, **AND**
  1. Has a family history of dementia that is consistent with an autosomal dominant pattern of inheritance, **AND**
     a. Has at least one relative with a history of early-onset Alzheimer disease, **OR**
- C. The member is symptomatic with dementia, **AND**
  1. Was diagnosed with dementia at 65 years of age or younger, **AND**
     a. Has a close relative diagnosed with dementia, **OR**
     b. Has an unknown family history (e.g., adoption), **OR**
  2. Was diagnosed with dementia at 66 years 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.

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

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

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

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

APOE Variant Analysis for Alzheimer's Disease

XVIII. *APOE* variant analysis (81401, 81479, S3852) may be considered **medically necessary** when:
- A. The member is being evaluated for treatment with monoclonal antibodies directed against aggregated forms of beta amyloid (such as Leqembi).

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

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS) Multigene Panel

XX. Multigene panel analysis to establish a genetic etiology of amyotrophic lateral sclerosis (ALS) (81179, 81403, 81404, 81405, 81406, 81407, 81479, S3800) may be considered **medically necessary** when **both** of the following are met:
- A. The member displays **all** of the following:
  1. Evidence of lower motor neuron (LMN) degeneration
  2. Evidence of upper motor neuron (UMN) degeneration
  3. Progressive spread of symptoms
  4. No evidence of other disease processes that could explain the LMN and UMN degeneration
- B. The panel includes, at a minimum, the following genes: *C9orf72*, *SOD1*, *FUS*, and *TARDBP*.

XXI. Multigene panel analysis to establish a genetic etiology of amyotrophic lateral sclerosis (ALS) (81179, 81403, 81404, 81405, 81406, 81407, 81479, S3800) is considered **investigational** for all other indications.

Duchenne And Becker Muscular Dystrophy
***DMD* Sequencing and/or Deletion/Duplication Analysis**

XXII. *DMD* sequencing and/or deletion/duplication analysis (81161, 81408, 0218U) to establish or confirm a diagnosis of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) may be considered **medically necessary** when **any** of the following are met:
- A. The member has **all** of the following clinical characteristics of DMD:
  1. Progressive symmetric muscular weakness - proximal greater than distal, often with calf hypertrophy (enlargement)
  2. Symptoms presenting before age five years
  3. Wheelchair dependency before age 13 years
  4. Elevated serum creatine kinase concentration, typically more than 10 times the normal levels
- B. The member has **all** of the following clinical characteristics of BMD:
  1. Elevated serum creatine kinase concentration, typically more than 5 times the normal levels, **AND**
     - a. At least **one** of the following:
       - i. Progressive symmetric muscle weakness (proximal more so than distal) often with calf hypertrophy (weakness of quadriceps femoris in some cases the only sign)
       - ii. Activity-induced cramping
       - iii. Flexion contractures of the elbows
       - iv. Wheelchair dependency after age 16 years
       - v. Preservation of neck flexor muscle strength
- C. The member is asymptomatic (male or female)
  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
- D. The member is an asymptomatic female, **AND**
  1. Has a first- or second-degree relative with a clinical diagnosis of Duchenne or Becker muscular dystrophy.

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

Facioscapulohumeral Muscular Dystrophy (FSHD)
D4Z4 Haplotype Analysis, and/or *SMCHD1* and *DNMT3B* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel

XXIV. D4Z4 haplotype analysis (81404), and/or *SMCHD1* (81479) and *DNMT3B* (81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81404, 81479) to establish or confirm a diagnosis of facioscapulohumeral muscular dystrophy may be considered **medically necessary** when:
- A. The member displays **any** of the following:
  1. Weakness (which is often asymmetric) that predominantly involves the facial, scapular stabilizer, or foot dorsiflexor muscles without associated ocular or bulbar muscle weakness
  2. Progression of weakness after pregnancy
  3. Prior diagnosis of inflammatory myopathy that was refractory to immunosuppression.

XXV. D4Z4 haplotype analysis (81404), and/or *SMCHD1* (81479) and *DNMT3B* sequencing and/or deletion/duplication analysis (81479) or multigene panel analysis (81404, 81479) to establish or confirm a diagnosis of facioscapulohumeral muscular dystrophy is considered **investigational** for all other indications.

Friedreich's Ataxia
***FXN* Repeat Analysis and/or Sequencing Analysis**

XXVI. *FXN* repeat analysis (81284, 81285, 0233U) and/or sequencing analysis (81286, 81404) to establish or confirm a diagnosis of Friedreich's Ataxia may be considered **medically necessary** when:
- A. The member has at least **two** of the following:
  1. Progressive ataxia of the gait and limbs (e.g., cerebellar ataxia), **OR**
  2. Dysarthria, **OR**
  3. Decrease in/loss of position sense and/or vibration sense in lower limbs, **OR**
  4. Pyramidal weakness of the legs, **OR**
  5. Extensor plantar responses/Babinski signs, **OR**
  6. Muscle weakness, **OR**
  7. Scoliosis, **OR**
  8. Pes cavus (flat feet), **OR**
  9. Hypertrophic nonobstructive cardiomyopathy, **OR**
  10. Glucose intolerance or diabetes mellitus, **OR**
  11. Optic atrophy and/or deafness, **AND**
- B. Non-genetic causes of ataxia have been ruled out (e.g., alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, tumors), **OR**
- C. The member is asymptomatic*, **AND**
  1. Has a biological sibling with Friedreich's ataxia.

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

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

Huntington's Disease
***HTT* Repeat Analysis**

XXVIII. *HTT* repeat analysis to establish a diagnosis or for predictive testing of Huntington's disease (HD) (81271, 81274) may be considered **medically necessary** when **any** of the following are met:
- A. The member displays clinical features of Huntington's disease (i.e, progressive motor disability featuring chorea, where voluntary movement may also be affected)
- B. The member has a clinical diagnosis of Huntington's Disease
- C. The member is undergoing predictive testing*, **AND** has **both** of the following:
  1. The member is presymptomatic/asymptomati
  2. The member is 18 years of age or older**, AND**
     - a. The member has a close relative with CAG trinucleotide repeat expansion of 27 or more in *HTT*, **OR**
     - b. The member has a first-degree relative with a clinical diagnosis of HD without prior genetic testing.

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

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

Inherited Peripheral Neuropathies (Examples: Charcot-Marie-Tooth Disease And Hereditary Neuropathy With Liability To Pressure Palsies)
***PMP22* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel**

XXX. *PMP22* sequencing and/or deletion/duplication analysis (81324, 81325) or multigene panel analysis (81448) to establish a genetic diagnosis of an inherited peripheral neuropathy may be considered **medically necessary** when:
- A. The member displays **one or more** of the following:
  1. Distal muscle weakness and atrophy
  2. Pes cavus foot deformity
  3. Weak ankle dorsiflexion
  4. Depressed tendon reflexes
  5. Recurrent acute focal sensory and motor neuropathies mainly at entrapment sites
  6. Painless nerve palsy after minor trauma or compression
  7. Evidence on physical examination of previous nerve palsy such as focal weakness, atrophy, or sensory loss
  8. Complete spontaneous recovery from neuropathies.

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

Limb-Girdle Muscular Dystrophy (LGMD)
Limb-girdle Muscular Dystrophy Multigene Panel

XXXII. Multigene panel analysis to establish a diagnosis of limb-girdle muscular dystrophy (81405, 81406, 81408, 81479) may be considered **medically necessary** when:
- A. The member displays slowly progressive, symmetrical weakness, **AND**
- B. The member has **any** of the following features:
  1. Limb-girdle pattern of weakness affecting proximal muscles of the arms and legs
  2. Scapuloperoneal weakness
  3. Distal weakness
  4. Elevated serum creatine kinase levels, **OR**
- C. The member is asymptomatic, **AND**
  1. The member has a close relative diagnosed with limb-girdle muscular dystrophy whose genetic status is unavailable.

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

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

XXXIV. *DMPK* repeat analysis (81234, 81239, 81401, 81404, S3853) and/or *CNBP* repeat analysis (81187, S3853) to establish a diagnosis of myotonic dystrophy may be considered **medically necessary** when:
- A. The member meets **either** of the following:
  1. The member is a neonate with **two or more** of the following:
     a. Hypotonia, **OR**
     b. Facial muscle weakness, **OR**
     c. Generalized weakness, **OR**
     d. Positional malformations, including clubfoot, **OR**
     e. Respiratory insufficiency, **OR**
  2. The member is any age and displays any **one** of the following:

a. Muscle weakness, especially of the distal leg., hand, neck, and face, **OR**
b. Myotonia, which often manifests as the inability to quickly release a hand grip (grip myotonia), **OR**
c. Posterior subcapsular cataracts, **OR**
d. Cardiac conduction defects or progressive cardiomyopathy, **OR**
e. Insulin insensitivity, **OR**
f. Hypogammaglobulinemia, **OR**

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

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

Hereditary Dystonia
Hereditary Dystonia Multigene Panel

XXXVI. Multigene panel analysis to establish a genetic diagnosis of hereditary dystonia (81404, 81405, 81406, 81407, 81408, 81479) may be considered **medically necessary** when:
A. The member has a clinical presentation consistent with dystonia or patterns of abnormal, repetitive, dystonic movements.

XXXVII. Multigene panel analysis to establish a genetic diagnosis of hereditary dystonia (81404, 81405, 81406, 81407, 81408, 81479) is considered **investigational** for all other indications.

Parkinson Disease
Parkinson Disease Multigene Panel

XXXVIII. Multigene panel testing (81479) to establish a genetic diagnosis of Parkinson disease may be considered **medically necessary** when **both** of the following are met:
A. The member has a clinical diagnosis of Parkinson disease
B. The member has a family history of Parkinson disease.

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

Hereditary Spastic Paraplegia
Hereditary Spastic Paraplegia Multigene Panel

XL. Multigene panel analysis to establish a genetic diagnosis of hereditary spastic paraplegia (81448) may be considered **medically necessary** when:
A. The member has **any** of the following:
1. Lower-extremity spasticity especially in hamstrings, quadriceps, adductors, and gastrocnemius-soleus muscles
2. Weakness especially in the iliopsoas, hamstring, and tibialis anterior
3. Lower-extremity hyperreflexia and extensor plantar responses
4. Mildly impaired vibration sensation in the distal lower extremities.

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

Congenital Myasthenic Syndromes
Congenital Myasthenic Syndromes Multigene Panel

XLII. Multigene panel analysis to establish a genetic diagnosis of congenital myasthenic syndromes (81406, 81407, 81479) may be considered **medically necessary** when:
A. The member has **any** of the following:

1. Neonatal respiratory insufficiency, with sudden episodic apnea and cyanosis
2. Neonatal joint contractures (e.g., arthrogryposis multiplex congenita)
3. Stridor, feeding difficulties, poor suck/cry, choking spells, eyelid ptosis, and/or facial, bulbar, or generalized weakness in neonates
4. Abnormal muscle fatigability/weakness
5. Delayed motor milestones
6. Eyelid ptosis or extraocular muscle weakness
7. Facial and bulbar weakness with nasal speech and difficulties in coughing and swallowing
8. Spinal deformity or muscle atrophy
9. Abnormal electromyography (EMG) testing showing a defect in neuromuscular transmission.

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

Myotonia Congenita
***CLCN1* Sequencing and/or Deletion/Duplication Analysis**

XLIV. *CLCN1* sequencing and/or deletion/duplication analysis (81406, 81479) to establish a genetic diagnosis of myotonia congenita may be considered **medically necessary** when:
   A. The member has **any** of the following:
      1. Episodes of muscle stiffness (myotonia) or cramps beginning in early childhood that are alleviated by brief exercise
      2. Myotonic contraction is elicited by percussion of muscles
      3. Electromyography (EMG) performed with needle electrodes discloses characteristic showers of spontaneous electrical activity (myotonic bursts).

XLV. *CLCN1* sequencing and/or deletion/duplication analysis (81406, 81479) to establish a genetic diagnosis of myotonia congenita is considered **investigational** for all other indications.

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

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

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

Other Covered Epilepsy, Neuromuscular, And Neurodegenerative Disorders

XLVIII. Genetic testing to establish or confirm one of the following epilepsy, neuromuscular, and neurodegenerative conditions to guide management may be considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II below):

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

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

*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.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

DEFINITIONS

1. **Close relatives** include first, second, and third degree blood relatives on the same side of the family:
   a. **First-degree relatives** are parents, siblings, and children
   b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
   c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins
2. **Early-onset Alzheimer disease** is defined as Alzheimer disease occurring in an individual under age 65
3. A **neonate** is a baby who is four weeks old or younger
4. **Childhood** is the period of development until the 18th birthday.
5. **Myotonia** is defined as impaired relaxation of skeletal muscle after voluntary contraction.
6. **Autosomal dominant** inheritance patterns are generally characterized by the following traits*:
   a. There are individuals with the condition in multiple generations of a family
   b. Individuals who do not have the condition do not have children with the condition
   c. Individuals with the condition have a parent with the condition

*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.

Description

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

Related Policies

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

- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing for tests intended to diagnose genetic conditions following amniocentesis, chorionic villus sampling, PUBS, or pregnancy loss.
- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for coverage criteria related to prenatal carrier screening, preimplantation testing of embryos, or preconception carrier screening (including carrier screening for Duchenne/Becker muscular dystrophy and SMA).
- ***Genetic Testing: Pharmacogenetics*** for coverage criteria related to genetic testing prior to the initiation of drug treatment with carbamazepine.
- ***Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders*** for coverage criteria related to genetic testing for mitochondrial disorders.
- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing.
- ***Genetic Testing: Preimplantation Genetic Testing*** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to epilepsy, neuromuscular, and neurodegenerative disorders not specifically discussed in this or another non-general policy.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

- N/A

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 (2020)

Winder et al published a study in 2020 in Neurology: Genetics, which reported results of genetic testing of 25,356 individuals who were suspected to have a neuromuscular disorder. Twenty percent of the cohort was found to have a definitive molecular diagnosis. (p. 3) The authors comment: "Multigene NGS [next generation sequencing] analysis advances the interpretation of heterogeneity for any single clinical disorder and also helps refine differential diagnoses. Panels can also be useful for individuals for whom a single-gene 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 (2021)

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

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.

Comprehensive Ataxia Panel

American College of Medical Genetics and Genomics (ACMG)

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

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

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

Spinal Muscular Atrophy

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

GeneReviews: Spinal Muscular Atrophy

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

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

Rett Syndrome - *MECP2* Sequencing and/or Deletion/Duplication Analysis

American College of Medical Genetics and Genomics (ACMG)

The American College of Medical Genetics and Genomics (2013) revised its evidence-based guidelines for clinical genetics evaluation of autism spectrum disorders. Testing for *MECP2* genetic variants was recommended as part of the diagnostic workup of females who present with an autistic phenotype. Routine *MECP2* testing in males with autism spectrum disorders was not recommended). However, geneticists should be alert to the features of *MECP2* duplications and consider *MECP2* duplication testing in boys with autism and such features. (p. 402)

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

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 coverage criteria. In rare situations, an epilepsy panel of less than 25 genes may be performed, in which case alternate coverage criteria should be used (please refer to Concert Genetics medical policy "General Approach to Genetic and Molecular Testing").

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

GeneReviews: CADASIL

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.
CADASIL should be suspected in individuals with unexplained white matter hyperintensities and a family history of stroke and/or vascular dementia; however, lack of an apparent family history of

CADASIL does not preclude the diagnosis. The following clinical signs and neuroimaging findings can be observed in CADASIL.
Clinical signs

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

Brain imaging

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

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

Alzheimer Disease - *PSEN1*, *PSEN2*, and *APP* Sequencing and/or Deletion/Duplication Analysis
American College of Medical Genetics and Genomics (ACMG) and National Society of Genetic Counselors (NSGC)
The American College of Medical Genetics jointly with the National Society of Genetic Counselors (2011) issued a joint practice guideline , which was reaffirmed and reclassified as a practice resource in 2019. These guidelines state that:

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

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

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

Alzheimer Disease - *APOE* Variant Analysis for Alzheimer's Disease
Food and Drug Administration (FDA)
In the "highlights of prescribing information" document created by the FDA for monoclonal antibodies treatment directed against aggregated forms of beta amyloid, including Leqembi, the following is recommended: "Patients treated with this class of medications, including Leqembi, who

are ApoE e4 homozygotes have a higher incidence of ARIA [amyloid related imaging abnormalities], including symptomatic and serious ARIA, compared to heterozygotes and noncarriers. Testing for ApoE e4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA." (p. 1)

Amyotrophic Lateral Sclerosis - Familial Amyotrophic Lateral Sclerosis (FALS) Multigene Panel

Roggenbuck, et al

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

GeneReviews: Amyotrophic Lateral Sclerosis Overview

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The recommendations for genetic testing for Amyotrophic Lateral Sclerosis are as follows:
It is estimated that about 10%-15% of individuals with ALS have genetic ALS. Some of the genetic forms of ALS may confer particular clinical characteristics, although intra- and interfamilial variability of age at onset and disease progression is common.

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

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

Duchenne and Becker Muscular Dystrophy - *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.

Facioscapulohumeral Muscular Dystrophy (FSHD) - *FSHD1* Deletion/Duplication or Haplotype Analysis and/or *SMCHD1* and *DNMT3B* Sequencing and/or Deletion Analysis or Multigene Panel

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

Friedreich's Ataxia - *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* of the following clinical features and family history:

- Neurologic findings, typically with onset before age 25 years**.
  - Progressive ataxia of gait and limbs
  - Dysarthria
  - Decrease in/loss of position sense and/or vibration sense in lower limbs ∘
  - Pyramidal weakness of the legs, extensor plantar responses
- Musculoskeletal features
  - Muscle weakness
  - Scoliosis
  - Pes cavus
- Hypertrophic non-obstructive cardiomyopathy
- Endocrinologic features
  - Glucose intolerance

    - Diabetes mellitus
- Optic atrophy and/or deafness
- Family history consistent with autosomal recessive inheritance Note: Absence of a family history of autosomal recessive inheritance does not preclude the diagnosis.

* Concert Genetics interprets a combination of these clinical features, here, to mean at least two.
** In atypical cases, onset may be delayed

Huntington's Disease - *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.

Inherited Peripheral Neuropathy (Charcot-Marie-Tooth and Hereditary Neuropathy with Liability to Pressure Palsies) - *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."

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 moved to the forefront of diagnostic investigations. Broad genetic testing should be obtained with an LGMD or neuromuscular gene panel, which analyzes multiple genes associated with LGMDs and other muscular dystrophies/myopathies.

Myotonic Dystrophy
***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 le.g., 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."

Hereditary Dystonia Multigene Panel

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

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

Parkinson Disease Multigene Panel

GeneReviews - Parkinson Disease Overview
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 Disease GeneReviews, establishing a specific genetic cause of Parkinson disease:

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

Gasser et al (2023)
This review article states the following: "The identification of disease-causing mutations or strong risk factors for Parkinson's disease in genes encoding proteins such as α-synuclein (*SNCA*), leucine-rich repeat kinase-2 (*LRRK2*), or glucocerebrosidase (*GBA1*) has led to a better understanding of the different components of disease pathogenesis. Many gene and mutation-specific targeted disease-modifying treatments are under development and several studies are underway. It is, therefore, important to raise awareness among patients and their families and to offer genetic testing, at least to those patients who are considering to participate in innovative trials." (p. 777)

Cook, et al. (2020)
In this analysis of the Parkinson's disease genetic testing market in 2020, the authors highlighted variability and lack of consensus among available gene panels, along with a lack of clear professional guidelines for clinicians: "There have been no specific guidelines regarding which genes should be tested in the clinical setting for Parkinson's disease (PD) or parkinsonism. We evaluated the types of

clinical genetic testing offered for PD.... The panels were notable for their differences in size, ranging from 5 to 62 genes. Five genes for variant query were included in all panels (*SNCA, PRKN, PINK-1, PARK7 (DJ1)*, and *LRRK2*). Notably, the addition of the *VPS35* and *GBA* genes was variable.... We have identified marked heterogeneity in commercial gene tests offered for PD, specifically for multigene panels... Our findings highlight the urgent need for expert opinion on which genes and variants commercial laboratory services should consider for general PD panels and other PD-related panels." (p. 107)

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.

Congenital Myasthenic Syndrome - Congenital Myasthenic Syndromes Multigene Panel
GeneReviews-Congenital Myasthenic Syndromes Overview
GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.
GeneReviews comments on the onset of myasthenic syndromes as follows:

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

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

Myotonia Congenita - *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.

Hypokalemic Periodic Paralysis - *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.

References

1. Tawil R, Kissel JT, Heatwole C, et al. Evidence-based guideline summary: Evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. *Neurology*. 2015;85(4):357-364. doi:10.1212/WNL.0000000000001783
2. Highlights of prescribing information: Leqembi. US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s000lbl.pdf. Accessed August 8, 2023.
3. Bird TD. Charcot-Marie-Tooth (CMT) Hereditary Neuropathy Overview. 1998 Sep 28 [Updated 2023 Feb 23]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1358/
4. Goldman, J., Hahn, S., Catania, J. *et al.* Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med* 13, 597–605 (2011). https://doi.org/10.1097/GIM.0b013e31821d69b8
5. Goldman, J.S., Hahn, S.E., Catania, J.W. *et al.* ADDENDUM: Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med* 21, 2404 (2019). https://doi.org/10.1038/s41436-019-0559-1
6. Narayanaswami P, Weiss M, Selcen D, et al. Evidence-based guideline summary: diagnosis and treatment of limb-girdle and distal dystrophies: report of the guideline development subcommittee of the American Academy of Neurology and the practice issues review panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. *Neurology*. 2014;83(16):1453-1463. doi:10.1212/WNL.0000000000000892
7. Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. 2000 Feb 24 [Updated 2020 Dec 03]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1352/.
8. "Genetic Testing of Minors for Adult-Onset Conditions". Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/genetic-testing-of-minors-for-adult-onset-conditions. Released February 15, 2017. Updated April 18, 2018.
9. Bidichandani SI, Delatycki MB. Friedreich Ataxia. 1998 Dec 18 [Updated 2017 Jun 1]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1281/.
10. Siddique N, Siddique T. Amyotrophic Lateral Sclerosis Overview. 2001 Mar 23 [Updated 2023 Sept 28]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1450/
11. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and

gastrointestinal and nutritional management [published correction appears in Lancet Neurol. 2018 Apr 4;:]. *Lancet Neurol*. 2018;17(3):251-267. doi:10.1016/S1474-4422(18)30024-3
12. Jayadev, S., Bird, T. Hereditary ataxias: overview. *Genet Med* 15, 673–683 (2013). https://doi.org/10.1038/gim.2013.28
13. Caron NS, Wright GEB, Hayden MR. Huntington Disease. 1998 Oct 23 [Updated 2020 Jun 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1305/
14. Chrestian N. Hereditary Neuropathy with Liability to Pressure Palsies. 1998 Sep 28 [Updated 2020 Aug 27]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1392/
15. Bird TD. Myotonic Dystrophy Type 1. 1999 Sep 17 [Updated 2021 Mar 25]. In: Adam MP, Everman DB, Mirzaa GM, et al, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1165/
16. Schoser B. Myotonic Dystrophy Type 2. 2006 Sep 21 [Updated 2020 Mar 19]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1466/
17. The Myotonic Dystrophy Foundation. Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type I (Published in 2018). Available at: https://www.myotonic.org/sites/default/files/MDF_2018_CareConsiderationsDM1_2019_1_4.pdf
18. The Myotonic Dystrophy Foundation. Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type II (Published November 5, 2019). Available at: https://www.myotonic.org/sites/default/files/pages/files/Myotonic-ClinicalCareRecs-AdultsDM2-2019-11-05.pdf
19. Klein C, Lohmann K, Marras C, et al. Hereditary Dystonia Overview. 2003 Oct 28 [Updated 2017 Jun 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1155/
20. Cook Shukla L, Schulze J, Farlow J, et al. Parkinson Disease Overview. 2004 May 25 [Updated 2019 Jul 25]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1223/
21. Hedera P. Hereditary Spastic Paraplegia Overview. 2000 Aug 15 [Updated 2021 Feb 11]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1509/
22. Abicht A, Müller J S, Lochmüller H. Congenital Myasthenic Syndromes. 2003 May 9 [Updated 2021 Dec 23]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1168/
23. Dunø M, Colding-Jørgensen E. Myotonia Congenita. 2005 Aug 3 [Updated 2021 Feb 25]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1355/
24. Weber F, Lehmann-Horn F. Hypokalemic Periodic Paralysis. 2002 Apr 30 [Updated 2018 Jul 26]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1338/
25. Preston MK, Tawil R, Wang LH. Facioscapulohumeral Muscular Dystrophy. 1999 Mar 8 [Updated 2020 Feb 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews

[Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1443/
26. Darras BT, Urion DK, Ghosh PS. Dystrophinopathies. 2000 Sep 5 [Updated 2022 Jan 20. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1119/
27. Kassardjian CD, Amato AA, Boon AJ, Childers MK, Klein CJ; AANEM Professional Practice Committee. The utility of genetic testing in neuromuscular disease: A consensus statement from the AANEM on the clinical utility of genetic testing in diagnosis of neuromuscular disease. Muscle Nerve. 2016;54(6):1007-1009. doi:10.1002/mus.25387
28. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
29. Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
30. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.
31. Nicolau S, Milone M, Liewluck T. Guidelines for genetic testing of muscle and neuromuscular junction disorders. Muscle Nerve. 2021 Sep;64(3):255-269. doi: 10.1002/mus.27337. Epub 2021 Jun 16. PMID: 34133031.
32. Smith L, Malinowski J, Ceulemans S, Peck K, Walton N, Sheidley BR, Lippa N. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. J Genet Couns. 2022 Oct 24. doi: 10.1002/jgc4.1646. Epub ahead of print. PMID: 36281494.
33. Gasser T. Genetic testing for Parkinson's disease in clinical practice. *J Neural Transm.* 2023; 130(6):777-782.
34. Winder TL, Tan CA, Klemm S, et al. Clinical utility of multigene analysis in over 25,000 patients with neuromuscular disorders. *Neurol Genet*. 2020;6(2):e412. Published 2020 Mar 9. doi:10.1212/NXG.0000000000000412
35. Prior TW; American College of Medical Genetics (ACMG) Laboratory Quality Assurance Committee. Technical standards and guidelines for myotonic dystrophy type 1 testing. *Genet Med*. 2009 (reaffirmed in 2015);11(7):552-555. doi:10.1097/GIM.0b013e3181abce0f
36. Kaur S, Christodoulou J. MECP2 Disorders. 2001 Oct 3 [Updated 2019 Sep 19]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1497/
37. Schaefer GB, Mendelsohn NJ; Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions [published correction appears in Genet Med. 2013 Aug;15(8):669]. Genet Med. 2013;15(5):399-407. doi:10.1038/gim.2013.32
38. Hack R, Rutten J, Lesnik Oberstein SAJ. CADASIL. 2000 Mar 15 [Updated 2019 Mar 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1500/
39. Huntington's Disease Society of America (HDSA). Genetic Testing Protocol for Huntington's Disease. 2016. http://hdsa.org/wp-content/uploads/2015/02/HDSA-Gen-Testing-Protocol-for-HD.pdf
40. Bryan ES, Alsaleem M. Myotonia Congenita. [Updated 2022 Aug 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562335/
41. Cook L, Schulze J, Verbrugge J, et al. The commercial genetic testing landscape for Parkinson's disease. Parkinsonism & Related Disorders. 2021;92:107-111.

42. Roggenbuck J, Eubank BHF, Wright J, et al. ; ALS Genetic Testing and Counseling Guidelines Expert Panel. Evidence-based consensus guidelines for ALS genetic testing and counseling [published online ahead of print, 2023 Sep 10]. *Ann Clin Transl Neurol*. 2023;10.1002/acn3.51895. doi:10.1002/acn3.51895
43. Daras BT et al. Limb-girdle Muscular Dystrophy [Updated Oct 2023]. In: UpToDate. https://www.uptodate.com/contents/limb-girdle-muscular-dystrophy#H387926787

Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier. The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0216U	Neurology (inherited ataxias), genomic DNA sequence analysis of 12 common genes including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants
	0217U	Neurology (inherited ataxias), genomic DNA sequence analysis of 51 genes including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants
	0218U	Neurology (muscular dystrophy), DMD gene sequence analysis, including small sequence changes, deletions, duplications, and variants

Type	Code	Description
		in non-uniquely mappable regions, blood or saliva, identification and characterization of genetic variants
	0233U	FXN (frataxin) (e.g., Friedreich ataxia), gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
	0234U	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	0236U	SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (e.g., spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications, deletions, and mobile element insertions
	81161	DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
	81179	ATXN2 (ataxin 2) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81185	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; full gene sequence
	81187	CNBP (CCHC-type zinc finger nucleic acid binding protein) (e.g., myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81189	CSTB (cystatin B) (e.g., Unverricht-Lundborg disease) gene analysis; full gene sequence
	81234	DMPK (DM1 protein kinase) (e.g., myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles
	81239	DMPK (DM1 protein kinase) (e.g., myotonic dystrophy type 1) gene analysis; characterization of alleles (e.g., expanded size)
	81271	HTT (huntingtin) (e.g., Huntington disease) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
	81274	HTT (huntingtin) (e.g., Huntington disease) gene analysis; characterization of alleles (e.g., expanded size)
	81284	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles
	81285	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; characterization of alleles (e.g., expanded size)
	81286	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; full gene sequence
	81302	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; full sequence analysis
	81303	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; known familial variant
	81304	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; duplication/deletion variants
	81324	PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
	81325	PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
	81329	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; dosage/deletion analysis (e.g., carrier testing),

Type	Code	Description
		includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
	81336	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; full gene sequence
	81400	Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81402	Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81407	Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
	81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
	81419	Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2
	81448	Hereditary peripheral neuropathies (e.g., Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (e.g., BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)
	81479	Unlisted molecular pathology procedure
HCPCS	S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)
	S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease
	S3853	Genetic testing for myotonic muscular dystrophy

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/01/2024	New policy.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language,

including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER**
New Policy **Policy Statement:** N/A	**Genetic Testing: Epilepsy, Neurodegenerative, and Neuromuscular Disorders BSC_CON_2.14** **Policy Statement:** **Comprehensive Neuromuscular Disorders Panel** I. Comprehensive neuromuscular panel analysis to establish a genetic diagnosis for a neuromuscular disorder (81161, 81404, 81405, 81406, 81479) may be considered **medically necessary** when **both** of the following are met: A. The member displays at least **one** of the following: 1. Neonatal respiratory insufficiency, with sudden episodic apnea and cyanosis 2. Neonatal joint contractures (e.g., arthrogryposis multiplex congenita) 3. Stridor, feeding difficulties, poor suck/cry, choking spells, eyelid ptosis, or facial, bulbar, or generalized weakness in neonates 4. Abnormal muscle fatigability/weakness 5. Delayed motor milestones 6. Eyelid ptosis or extraocular muscle weakness 7. Facial and bulbar weakness with nasal speech and difficulties in coughing and swallowing 8. Spinal deformity or muscle atrophy, 9. Abnormal electromyography (EMG) testing showing a defect in neuromuscular transmission B. **One** of the following: 1. The member's presentation is not consistent with a neuromuscular disorder for which targeted or single-gene analysis (e.g., *SMN1, DMD, PMP22*) is appropriate 2. The member underwent targeted or single-gene analysis for a neuromuscular disorder (e.g., *SMN1, DMD, PMP22*) and the results were non-diagnostic.

POLICY STATEMENT	
BEFORE	**AFTER**
	II. Comprehensive neuromuscular panel analysis to establish a genetic diagnosis for a neuromuscular disorder (81161, 81404, 81405, 81406, 81479) is considered **investigational** for all other indications. **Comprehensive Ataxia Panel** III. Comprehensive ataxia panel analysis to establish a genetic diagnosis of an ataxia (81185, 81189, 81286, 81403, 81404, 81479, 0216U, 0217U) may be considered **medically necessary** when **both** of the following are met: A. The member displays **one or more** of the following: 1. Poorly coordinated gait and finger/hand movements 2. Weakness of the eye muscles (ophthalmoplegia) 3. Dysarthria 4. Eye movement abnormalities (nystagmus, abnormal saccade movements) 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). IV. Comprehensive ataxia panel analysis to establish a genetic diagnosis of an ataxia (81185, 81189, 81286, 81403, 81404, 81479, 0216U, 0217U) is considered **investigational** for all other indications. **Spinal Muscular Atrophy** ***SMN1* Sequencing and/or Deletion/Duplication Analysis** V. *SMN1* sequencing and/or deletion/duplication analysis (81329, 81336, 81401, 81405, 0236U) to establish or confirm a diagnosis of spinal muscular atrophy may be considered **medically necessary** when **either** of the following are met: A. The member has a positive newborn screen for SMA B. The member has **any** of the following: 1. History of motor difficulties, especially with loss of skills 2. Proximal to distal muscle weakness 3. Hypotonia 4. Areflexia/hyporeflexia

POLICY STATEMENT	
BEFORE	**AFTER**
	5. Tongue fasciculations 6. Hand tremor 7. Recurrent lower respiratory tract infections or severe bronchiolitis in the first few months of life 8. Evidence of motor unit disease on electromyogram. VI. *SMN1* sequencing and/or deletion/duplication analysis (81329, 81336, 81401, 81405, 0236U) to establish or confirm a diagnosis of spinal muscular atrophy is considered **investigational** for all other indications. ***SMN2* Deletion/Duplication Analysis** VII. *SMN2* deletion/duplication analysis (81401) may be considered **medically necessary** when: A. The member has a diagnosis of spinal muscular atrophy. VIII. *SMN2* deletion/duplication analysis (81401) is considered **investigational** for all other indications. **Rett Syndrome** ***MECP2* Sequencing and/or Deletion/Duplication Analysis** IX. *MECP2* sequencing and/or deletion/duplication analysis (81302, 81304, 0234U) to establish or confirm a diagnosis of Rett syndrome may be considered **medically necessary** when **all** of the following are met: A. The member experienced a period of developmental regression (range: ages 1-4 years) followed by recovery or stabilization (range: ages 2-10 years) B. The member has at least **one** of the following: 1. Partial or complete loss of acquired purposeful hand skills 2. Partial or complete loss of acquired spoken language or language skill (e.g., babble) 3. Gait abnormalities: impaired (dyspraxic) or absence of ability 4. Stereotypic hand movements including hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms

POLICY STATEMENT	
BEFORE	**AFTER**
	C. The member does **not** have **either** of the following: 1. Brain injury secondary to peri- or postnatal trauma, neurometabolic disease, or severe infection that causes neurological problems 2. Grossly abnormal psychomotor development in the first six months of life, with early milestones not being met. X. *MECP2* sequencing and/or deletion/duplication analysis (81302, 81304, 0234U) to establish or confirm a diagnosis of Rett syndrome is considered **investigational** for all other indications. **Epilepsy** **Epilepsy Multigene Panel** XI. The use of an epilepsy multigene panel (81185, 81189, 81302, 81406, 81419, 81479) may be considered **medically necessary** when: B. The member has a history of unexplained epilepsy (i.e., seizures not caused by acquired etiology such as trauma, infection, structural brain abnormality, and/or stroke). XII. The use of an epilepsy multigene panel (81185, 81189, 81302, 81406, 81419, 81479) is considered **investigational** for all other indications. **CADASIL** ***NOTCH3* Sequencing and/or Deletion/Duplication Analysis** XIII. *NOTCH3* sequencing and/or deletion/duplication analysis (81406, 81479) to establish or confirm a diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) may be considered **medically necessary** when **any** of the following are met: A. The member has a family history of stroke and/or vascular dementia consistent with an autosomal dominant pattern of inheritance, **OR** B. The member has at least **one** of the following clinical features of CADASIL: 1. Transient ischemic attacks and ischemic stroke

POLICY STATEMENT	
BEFORE	**AFTER**
	2. Cognitive impairment, manifesting initially with executive dysfunction, with a concurrent stepwise deterioration due to recurrent strokes to vascular dementia 3. Migraine with aura (mean age of onset of 30 years) 4. Psychiatric disturbances, most frequently mood disturbances and apathy C. The member has at least **one** of the following brain imaging findings of CADASIL: 1. Symmetric and progressive white matter hyperintensities, often involving the anterior temporal lobes and external capsules 2. Lacunes of presumed vascular origin 3. Recent subcortical infarcts 4. Dilated perivascular spaces, sometimes referred to as subcortical lacunar lesions 5. Brain atrophy 6. Cerebral microbleeds. XIV. *NOTCH3* sequencing and/or deletion/duplication analysis (81406, 81479) to establish or confirm a diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is considered **investigational** for all other indications. **ALZHEIMER DISEASE** ***PSEN1*, *PSEN2*, and *APP* Sequencing and/or Deletion/Duplication Analysis** XV. *PSEN1* (81405, 81479), *PSEN2* (81406, 81479), and/or *APP* (81406, 81479) sequencing and/or deletion/duplication analysis to establish a diagnosis or determine future risk to develop early-onset Alzheimer disease may be considered **medically necessary** when: A. The member is 18 years of age or older, **AND** B. The member is asymptomatic*, **AND** 1. Has a family history of dementia that is consistent with an autosomal dominant pattern of inheritance, **AND** a. Has at least one relative with a history of early-onset Alzheimer disease, **OR**

POLICY STATEMENT	
BEFORE	**AFTER**
	C. The member is symptomatic with dementia, **AND** 1. Was diagnosed with dementia at 65 years of age or younger, **AND** a. Has a close relative diagnosed with dementia, **OR** b. Has an unknown family history (e.g., adoption), **OR** 2. Was diagnosed with dementia at 66 years 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. XVI. Genetic testing for Alzheimer's disease via other genes is considered **investigational.**** XVII. *PSEN1* (81405, 81479), *PSEN2* (81406, 81479), and/or *APP* (81406, 81479) sequencing and/or deletion/duplication analysis to establish the diagnosis or determine future risk to develop early-onset Alzheimer disease is considered **investigational** for all other indications. *Predictive testing should only be performed in the setting and context of thorough pre- and post-test counseling **Please see clinical guidelines "*APOE* Variant Analysis for Alzheimer's Disease" for coverage criteria for *APOE* testing ***APOE* Variant Analysis for Alzheimer's Disease** XVIII. *APOE* variant analysis (81401, 81479, S3852) may be considered **medically necessary** when: A. The member is being evaluated for treatment with monoclonal antibodies directed against aggregated forms of beta amyloid (such as Leqembi). XIX. *APOE* variant analysis (81401, 81479, S3852) is considered **investigational** for all other indications **Amyotrophic Lateral Sclerosis (ALS)**

POLICY STATEMENT	
BEFORE	**AFTER**
	Amyotrophic Lateral Sclerosis (ALS) Multigene Panel XX. Multigene panel analysis to establish a genetic etiology of amyotrophic lateral sclerosis (ALS) (81179, 81403, 81404, 81405, 81406, 81407, 81479, S3800) may be considered **medically necessary** when **both** of the following are met: A. The member displays **all** of the following: 1. Evidence of lower motor neuron (LMN) degeneration 2. Evidence of upper motor neuron (UMN) degeneration 3. Progressive spread of symptoms 4. No evidence of other disease processes that could explain the LMN and UMN degeneration B. The panel includes, at a minimum, the following genes: *C9orf72*, *SOD1*, *FUS*, and *TARDBP*. XXI. Multigene panel analysis to establish a genetic etiology of amyotrophic lateral sclerosis (ALS) (81179, 81403, 81404, 81405, 81406, 81407, 81479, S3800) is considered **investigational** for all other indications. **Duchenne And Becker Muscular Dystrophy** ***DMD* Sequencing and/or Deletion/Duplication Analysis** XXII. *DMD* sequencing and/or deletion/duplication analysis (81161, 81408, 0218U) to establish or confirm a diagnosis of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) may be considered **medically necessary** when **any** of the following are met: A. The member has **all** of the following clinical characteristics of DMD: 1. Progressive symmetric muscular weakness - proximal greater than distal, often with calf hypertrophy (enlargement) 2. Symptoms presenting before age five years 3. Wheelchair dependency before age 13 years 4. Elevated serum creatine kinase concentration, typically more than 10 times the normal levels B. The member has **all** of the following clinical characteristics of BMD:

POLICY STATEMENT	
BEFORE	**AFTER**
	1. Elevated serum creatine kinase concentration, typically more than 5 times the normal levels, **AND** a. At least **one** of the following: i. Progressive symmetric muscle weakness (proximal more so than distal) often with calf hypertrophy (weakness of quadriceps femoris in some cases the only sign) ii. Activity-induced cramping iii. Flexion contractures of the elbows iv. Wheelchair dependency after age 16 years v. Preservation of neck flexor muscle strength C. The member is asymptomatic (male or female) 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 D. The member is an asymptomatic female, **AND** 1. Has a first- or second-degree relative with a clinical diagnosis of Duchenne or Becker muscular dystrophy. XXIII. *DMD* sequencing and/or deletion/duplication analysis (81161, 81408, 0218U) to establish a diagnosis of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) is considered **investigational** for all other indications. **Facioscapulohumeral Muscular Dystrophy (FSHD)** **D4Z4 Haplotype Analysis, and/or *SMCHD1* and *DNMT3B* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel** XXIV. D4Z4 haplotype analysis (81404), and/or *SMCHD1* (81479) and *DNMT3B* (81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81404, 81479) to establish or confirm a diagnosis of facioscapulohumeral muscular dystrophy may be considered **medically necessary** when: A. The member displays **any** of the following: 1. Weakness (which is often asymmetric) that predominantly involves the facial, scapular stabilizer, or foot dorsiflexor

POLICY STATEMENT	
BEFORE	**AFTER**
	muscles without associated ocular or bulbar muscle weakness 2. Progression of weakness after pregnancy 3. Prior diagnosis of inflammatory myopathy that was refractory to immunosuppression. XXV. D4Z4 haplotype analysis (81404), and/or *SMCHD1* (81479) and *DNMT3B* sequencing and/or deletion/duplication analysis (81479) or multigene panel analysis (81404, 81479) to establish or confirm a diagnosis of facioscapulohumeral muscular dystrophy is considered **investigational** for all other indications. **Friedreich's Ataxia** ***FXN* Repeat Analysis and/or Sequencing Analysis** XXVI. *FXN* repeat analysis (81284, 81285, 0233U) and/or sequencing analysis (81286, 81404) to establish or confirm a diagnosis of Friedreich's Ataxia may be considered **medically necessary** when: A. The member has at least **two** of the following: 1. Progressive ataxia of the gait and limbs (e.g., cerebellar ataxia), **OR** 2. Dysarthria, **OR** 3. Decrease in/loss of position sense and/or vibration sense in lower limbs, **OR** 4. Pyramidal weakness of the legs, **OR** 5. Extensor plantar responses/Babinski signs, **OR** 6. Muscle weakness, **OR** 7. Scoliosis, **OR** 8. Pes cavus (flat feet), **OR** 9. Hypertrophic nonobstructive cardiomyopathy, **OR** 10. Glucose intolerance or diabetes mellitus, **OR** 11. Optic atrophy and/or deafness, **AND** B. Non-genetic causes of ataxia have been ruled out (e.g., alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, tumors), **OR** C. The member is asymptomatic*, **AND** 1. Has a biological sibling with Friedreich's ataxia.

POLICY STATEMENT	
BEFORE	**AFTER**
	XXVII. *FXN* repeat analysis (81284, 81285, 0233U) and/or sequencing analysis (81286, 81404) to establish or confirm a diagnosis of Friedreich's Ataxia is considered **investigational** for all other indications. * Predictive testing should only be performed in the setting and context of thorough pre- and post-test counseling **Huntington's Disease** ***HTT* Repeat Analysis** XXVIII. *HTT* repeat analysis to establish a diagnosis or for predictive testing of Huntington's disease (HD) (81271, 81274) may be considered **medically necessary** when **any** of the following are met: A. The member displays clinical features of Huntington's disease (i.e, progressive motor disability featuring chorea, where voluntary movement may also be affected) B. The member has a clinical diagnosis of Huntington's Disease C. The member is undergoing predictive testing*, **AND** has **both** of the following: 1. The member is presymptomatic/asymptomati 2. The member is 18 years of age or older**, AND** a. The member has a close relative with CAG trinucleotide repeat expansion of 27 or more in *HTT*, **OR** b. The member has a first-degree relative with a clinical diagnosis of HD without prior genetic testing. XXIX. *HTT* repeat analysis to establish a diagnosis or for predictive testing of Huntington's disease (HD) (81271, 81274) is considered **investigational** for all other indications. * Predictive testing should only be performed in the setting and context of thorough pre- and post-test counseling. **Inherited Peripheral Neuropathies (Examples: Charcot-Marie-Tooth Disease And Hereditary Neuropathy With Liability To Pressure Palsies)** ***PMP22* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel**

POLICY STATEMENT	
BEFORE	**AFTER**
	XXX. *PMP22* sequencing and/or deletion/duplication analysis (81324, 81325) or multigene panel analysis (81448) to establish a genetic diagnosis of an inherited peripheral neuropathy may be considered **medically necessary** when: A. The member displays **one or more** of the following: 1. Distal muscle weakness and atrophy 2. Pes cavus foot deformity 3. Weak ankle dorsiflexion 4. Depressed tendon reflexes 5. Recurrent acute focal sensory and motor neuropathies mainly at entrapment sites 6. Painless nerve palsy after minor trauma or compression 7. Evidence on physical examination of previous nerve palsy such as focal weakness, atrophy, or sensory loss 8. Complete spontaneous recovery from neuropathies. XXXI. *PMP22* sequencing and/or deletion/duplication analysis (81324, 81325) or multigene panel analysis (81448) to establish a genetic diagnosis of an inherited peripheral neuropathy is considered **investigational** for all other indications. **Limb-Girdle Muscular Dystrophy (LGMD)** **Limb-girdle Muscular Dystrophy Multigene Panel** XXXII. Multigene panel analysis to establish a diagnosis of limb-girdle muscular dystrophy (81405, 81406, 81408, 81479) may be considered **medically necessary** when: A. The member displays slowly progressive, symmetrical weakness, **AND** B. The member has **any** of the following features: 1. Limb-girdle pattern of weakness affecting proximal muscles of the arms and legs 2. Scapuloperoneal weakness 3. Distal weakness 4. Elevated serum creatine kinase levels, **OR** C. The member is asymptomatic, **AND** 1. The member has a close relative diagnosed with limb-girdle muscular dystrophy whose genetic status is unavailable.

POLICY STATEMENT	
BEFORE	**AFTER**
	XXXIII. Multigene panel analysis to establish a diagnosis of limb-girdle muscular dystrophy (81405, 81406, 81408, 81479) is considered **investigational** for all other indications. **Myotonic Dystrophy** ***DMPK* and/or *CNBP* (*ZNF9*) Repeat Analysis** XXXIV. *DMPK* repeat analysis (81234, 81239, 81401, 81404, S3853) and/or *CNBP* repeat analysis (81187, S3853) to establish a diagnosis of myotonic dystrophy may be considered **medically necessary** when: A. The member meets **either** of the following: 1. The member is a neonate with **two or more** of the following: a. Hypotonia, **OR** b. Facial muscle weakness, **OR** c. Generalized weakness, **OR** d. Positional malformations, including clubfoot, **OR** e. Respiratory insufficiency, **OR** 2. The member is any age and displays any **one** of the following: a. Muscle weakness, especially of the distal leg, hand, neck, and face, **OR** b. Myotonia, which often manifests as the inability to quickly release a hand grip (grip myotonia), **OR** c. Posterior subcapsular cataracts, **OR** d. Cardiac conduction defects or progressive cardiomyopathy, **OR** e. Insulin insensitivity, **OR** f. Hypogammaglobulinemia, **OR** B. The member is asymptomatic, **AND** 1. The member is 18 years of age or older, **AND** 2. The member has a first-degree relative with Myotonic dystrophy type 1 or 2. XXXV. *DMPK* repeat analysis (81234, 81239, 81401, 81404, S3853) and *CNBP* repeat analysis (81187, S3853) to establish a diagnosis of myotonic dystrophy is considered **investigational** for all other indications.

POLICY STATEMENT	
BEFORE	**AFTER**
	Hereditary Dystonia **Hereditary Dystonia Multigene Panel** XXXVI. Multigene panel analysis to establish a genetic diagnosis of hereditary dystonia (81404, 81405, 81406, 81407, 81408, 81479) may be considered **medically necessary** when: A. The member has a clinical presentation consistent with dystonia or patterns of abnormal, repetitive, dystonic movements. XXVII. Multigene panel analysis to establish a genetic diagnosis of hereditary dystonia (81404, 81405, 81406, 81407, 81408, 81479) is considered **investigational** for all other indications. **Parkinson Disease** **Parkinson Disease Multigene Panel** XXVIII. Multigene panel testing (81479) to establish a genetic diagnosis of Parkinson disease may be considered **medically necessary** when **both** of the following are met: A. The member has a clinical diagnosis of Parkinson disease B. The member has a family history of Parkinson disease. XXIX. Multigene panel testing (81479) to establish a genetic diagnosis of Parkinson disease is considered **investigational** for all other indications. **Hereditary Spastic Paraplegia** **Hereditary Spastic Paraplegia Multigene Panel** XL. Multigene panel analysis to establish a genetic diagnosis of hereditary spastic paraplegia (81448) may be considered **medically necessary** when: A. The member has **any** of the following: 1. Lower-extremity spasticity especially in hamstrings, quadriceps, adductors, and gastrocnemius-soleus muscles 2. Weakness especially in the iliopsoas, hamstring, and tibialis anterior

POLICY STATEMENT	
BEFORE	**AFTER**
	3. Lower-extremity hyperreflexia and extensor plantar responses 4. Mildly impaired vibration sensation in the distal lower extremities. XLI. Multigene panel analysis to establish a genetic diagnosis of hereditary spastic paraplegia (81448) is considered **investigational** for all other indications. **Congenital Myasthenic Syndromes** **Congenital Myasthenic Syndromes Multigene Panel** XLII. Multigene panel analysis to establish a genetic diagnosis of congenital myasthenic syndromes (81406, 81407, 81479) may be considered **medically necessary** when: A. The member has **any** of the following: 1. Neonatal respiratory insufficiency, with sudden episodic apnea and cyanosis 2. Neonatal joint contractures (e.g., arthrogryposis multiplex congenita) 3. Stridor, feeding difficulties, poor suck/cry, choking spells, eyelid ptosis, and/or facial, bulbar, or generalized weakness in neonates 4. Abnormal muscle fatigability/weakness 5. Delayed motor milestones 6. Eyelid ptosis or extraocular muscle weakness 7. Facial and bulbar weakness with nasal speech and difficulties in coughing and swallowing 8. Spinal deformity or muscle atrophy 9. Abnormal electromyography (EMG) testing showing a defect in neuromuscular transmission. XLIII. Multigene panel analysis to establish a genetic diagnosis of congenital myasthenic syndromes (81406, 81407, 81479) is considered **investigational** for all other indications. **Myotonia Congenita** ***CLCN1* Sequencing and/or Deletion/Duplication Analysis**

POLICY STATEMENT	
BEFORE	**AFTER**
	XLIV. *CLCN1* sequencing and/or deletion/duplication analysis (81406, 81479) to establish a genetic diagnosis of myotonia congenita may be considered **medically necessary** when: A. The member has **any** of the following: 1. Episodes of muscle stiffness (myotonia) or cramps beginning in early childhood that are alleviated by brief exercise 2. Myotonic contraction is elicited by percussion of muscles 3. Electromyography (EMG) performed with needle electrodes discloses characteristic showers of spontaneous electrical activity (myotonic bursts). XLV. *CLCN1* sequencing and/or deletion/duplication analysis (81406, 81479) to establish a genetic diagnosis of myotonia congenita is considered **investigational** for all other indications. **Hypokalemic Periodic Paralysis** ***CACNA1S* and *SCN4A* Sequencing and/or Deletion/Duplication Analysis, or Periodic Paralysis Multigene Panel** XLVI. *CACNA1S* and *SCN4A* sequencing and/or deletion/duplication analysis, or Periodic Paralysis Multigene Panel (81406, 81479) to establish a genetic diagnosis of periodic paralysis may be considered **medically necessary** when: A. Alternative causes of hypokalemia have been excluded (e.g., renal, adrenal, thyroid dysfunction; renal tubular acidosis; diuretic and laxative abuse), **AND** B. The member has had two or more attacks of muscle weakness with documented serum potassium less than 3.5 mEq/L, **OR** C. The member has had one attack of muscle weakness, **AND** 1. Has a close relative who has had one attack of muscle weakness with documented serum potassium less than 3.5 mEq/L, **OR** D. The member has three or more of the following features: 1. Onset of symptoms in the first or second decade, **OR** 2. Muscle weakness involving at least 1 limb lasting longer than two hours, **OR**

POLICY STATEMENT	
BEFORE	**AFTER**
	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. XLVII. *CACNA1S* and *SCN4A* sequencing and/or deletion/duplication analysis, or Periodic Paralysis Multigene Panel (81406, 81479) to establish a genetic diagnosis of periodic paralysis is considered **investigational** for all other indications. **Other Covered Epilepsy, Neuromuscular, And Neurodegenerative Disorders** XLVIII. Genetic testing to establish or confirm one of the following epilepsy, neuromuscular, and neurodegenerative conditions to guide management may be considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II below): A. AADC deficiency B. Hereditary Transthyretin Amyloidosis C. X-linked Adrenoleukodystrophy D. L1 Syndrome E. SCN9A Neuropathic Pain Syndromes F. Cerebral Cavernous Malformation, Familial G. STAC3 Disorder. XLIX. Genetic testing to establish or confirm the diagnosis of all other epilepsy, neurodegenerative, and neuromuscular disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *General Approach to Genetic and Molecular Testing* (see policy for coverage criteria). *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.