Clinical Policy: Genetic Testing Epilepsy, Neurodegenerative, and Neuromuscular Disorders

Reference Number: CP.MP.218
Date of Last Revision: 02/22

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Genetic testing for hereditary epilepsy, neurodegenerative, and neuromuscular disorders may be used to confirm a diagnosis in a patient who has signs and/or symptoms of the disease, but conventional diagnostic methods have been unsuccessful. Confirming the diagnosis may alter some aspects of management and may eliminate the need for further diagnostic workup. This document addresses genetic testing for neurodegenerative and neuromuscular genetic diseases.

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81403, 81326, 81337	Targeted Mutation Analysis for a Known Familial Variant	Known Familial Variant Analysis	N/A
81479, 81443	Comprehensive Neuromuscular Disorders Panel (PerkinElmer Genomics) Comprehensive Neuromuscular Panel (PreventionGenetics) Neuromuscular NGS Panel (Sequencing & Deletion/Cupkication) (Fulgent Genetics) Neuromuscular Disorders Panel (GeneDx)	Comprehensive Neuromuscular Disorders Panel	G12, G13, G23-G26, G31, G32, G36, G37
0216U	Genomic Unity Ataxia Repeat Expansion Analysis (Variantyx, IInc.)	Comprehensive Ataxia Panel	G11.1, G11.19, G11.8, G11.96, Z82.0
0217U	Genomic Unity Comprehensive Ataxia Analysis (Variantyx, Inc.)	Comprehensive Ataxia Panel	G11.1, G11.19, G11.8, G11.96, Z82.0

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81343, 81344, 81401, 81479, 81443	Comprehensive Spinocerebellar Ataxia Repeat Expansion Panel (MNG Laboratories) Comprehensive Spinocerebellar Ataxia Repeat Expansion Panel, (LabCorp)	Comprehensive Ataxia Panel	G11.1, G11.19, G11.8, G11.96, Z82.0
81329, 81401	SMN1 Deletion/Duplication Analysis	SMN1 Sequencing and/or Deletion/Duplication Analysis	G12, Z84.41
0236U	SMN1 Deletion/Duplication Analysis	SMN1 Sequencing and/or Deletion/Duplication Analysis	G12, Z84.41
81336, 81405	SMN1 Sequencing Analysis	SMN1 Sequencing and/or Deletion/Duplication Analysis	G12, Z84.41
81401, 81403, 81404, 81405, 81406, 81407, 81419	Childhood-Onset Epilepsy Panel, ARUP Laboratories Infantile-Onset Epilepsy Panel, ARUP Laboratories Infantile Onset Epilepsy Panel, GeneDx Childhood Onset Epilepsy Panel, GeneDx	Epilepsy Multigene Panel	G40.001-G40.919
81405, S3855	PSEN1 targeted mutation analysis	PSEN1, PSEN2 and APP Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	F03, G30, G31.1, R41.0, R41.81, Z13.858, Z82.0, Z84.81
81406	PSEN2 targeted mutation analysis	PSEN1, PSEN2 and APP Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	F03, G30, G31.1, R41.0, R41.81, Z13.858, Z82.0, Z84.81
81406	APP targeted mutation analysis	PSEN1, PSEN2 and APP Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	F03, G30, G31.1, R41.0, R41.81, Z13.858, Z82.0, Z84.81

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81405, 81406, S3855	Early-Onset Alzheimer's Panel, Sequencing (ARUP Laboratories) Early Onset Familial Alzeheimer Disease (EOFAD) NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics) Alzheimer Disease, Familial, Panel (PreventionGenetics)	PSEN1, PSEN2 and APP Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	F03, G30, G31.1, R41.0, R41.81, Z13.858, Z82.0, Z84.81
81401, S3852	APOE Sequencing Analysis APOE Deletion/Duplication Analysis	APOE, TREM2, and Others Variant Analysis	N/A
81479	TREM2 Sequencing Analysis TREM 2 Deletion/Duplication Analysis	APOE, TREM2, and Others Variant Analysis	N/A
81404, 81405, 81406, 81479, S3800	Amyotrophic lateral sclerosis and related disorders NGS Panel - Comprehensive, (CTGT) Amyotrophic Lateral Sclerosis Panel, (PreventionGenetics)	ALS Multigene Panel	G12.21
81161	DMD Deletion/Duplication Analysis	DMD Sequencing and/or Deletion/Duplication Analysis	G71.01, R62.59, Z84.81
81408	DMD Sequencing Analysis	DMD Sequencing and/or Deletion/Duplication Analysis	G71.01, R62.59, Z84.81

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
0218U	Genomic Unity DMD Analysis (Variantyx, Inc.)	DMD Sequencing and/or Deletion/Duplication Analysis	G71.01, R62.59, Z84.81
81404	FSHMD1A Deletion/Duplication Analysis	FSHMD1A deletion/duplication or laplotype analysis, and/or SMCHD1 and DNMT3B sequencing and/or deletion/duplication analysis or Multigene Panel	G71.02, Z84.81
81404	FSHMD1A Haplotype Analysis	FSHMD1A deletion/duplication or laplotype analysis, and/or SMCHD1 and DNMT3B sequencing and/or deletion/duplication analysis or Multigene Panel	G71.02, Z84.81
81479	SMCHD1 Sequencing SMCHD1 Deletion/Duplication Analysis	FSHMD1A deletion/duplication or laplotype analysis, and/or SMCHD1 and DNMT3B sequencing and/or deletion/duplication analysis or Multigene Panel	G71.02, Z84.81
81404, 81479	FSHD-(FSHD1 & FSHD2) Detection of Abnormal Alleles with Interpretation - Full Test Panel (University of Iowa Hospitals and Clinics - Department of Pathology)	FSHMD1A deletion/duplication or laplotype analysis, and/or SMCHD1 and DNMT3B sequencing and/or deletion/duplication analysis or Multigene Panel	G71.02, Z84.81
81284, 81285, 82189, 81401	FXN Repeat Analysis	FXN Repeat Analysis and/or Sequencing Analysis	G11, Z84.81
81286, 81401	FXN Sequencing Analysis	FXN Repeat Analysis and/or Sequencing Analysis	G11, Z84.81
0233U	Genomic Unity FXN Analysis (Variantyx Inc)	FXN Repeat Analysis and/or Sequencing Analysis	G11, Z84.81
81271, 81274, 81404	HTT Repeat Analysis	HTT Repeat Analysis	G10, Z84.81

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81324, 81325	PMP22 Sequencing Analysis PMP22 Deletion/Duplication Analysis	PMP22 Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	G60.0, G60.8, G60.9
81403, 81404, 81405, 81406, 81448, 81479	Charcot-Marie Tooth disease NGS Panel (CTGT) Charcot-Marie Tooth Comprehensive Panel (PreventionGenetics) Hereditary Neuropathy Panel (GeneDx)	PMP22 Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	G60.0, G60.8, G60.9
81400, 81404, 81405, 81406, 81408, 81479	Limb-Girdle Muscular Dystrophy NGS Panel (CTGT) Limb-Girdle Muscular Panel (GeneDx) Limb-Girdle Muscular Dystrophy (LGMD) Panel (Prevention Genetics) Invitae Limb-Girdle Muscular Dystrophy Panel (Invitae) Limb-Girdle Muscular Dystrophy (MNG Laboratories)	LGMD Multigene Panel	G71.0, Z13.71, Z82.0, Z84.81
81234, 81239, 81401, 81404, S3853	DMPK Repeat Analysis	DMPLK and/or CNBP Repeat Analysis	G71.11, Z84.81
81187, 81401, S3853	CNBP Repeat Analysis	DMPLK and/or CNBP Repeat Analysis	G71.11, Z84.81
81400, 81404, 81405, 81406, 81443	Dystonia Panel, GeneDx Dystonia Panel, Prevention Genetics Invitae	Dystonia Multigene Panel	G24.1, G24.9

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
	Dystonia Comprehensive Panel, Invitae		
81402, 81408	LRRK2 Sequencing Analysis LRRK2 Deletion/Duplication Analysis	GBA, LRRK2, SCNA, and VPS35 Sequencing and/or Deletion/Duplication Analysis	G20
81479	GBA Sequencing Analysis SCNA Sequencing Analysis VPS35 Sequencing Analysis	GBA, LRRK2, SCNA, and VPS35 Sequencing and/or Deletion/Duplication Analysis	G20
81405, 81406, 81407, 81448, 81479	Invitae Hereditary Spastic Paraplegia Comprehensive Panel, Invitae Complex Hereditary Spastic Paraplegia Panel, Prevention Genetics Comprehensive Hereditary Spastic Paraplegia Panel, GeneDx	Spastic Paraplegia Multigene Panel	G11.4, G82.2
81443, 81479	Congenital Myasthenic Syndrome Panel, Prevention Genetics Invitae Congenital Myasthenic Syndrome Panel, Invitae	Congenital Myasthenic Multigene Panel	G70.2
81406	Myotonia Congenita via the *CLCN1* gene, Prevention Genetics	CLCN1 Sequencing and/or Deletion/Duplication Analysis	G71.12

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81406, 81479	*CACNA1S* gene analysis *SCN4A* gene analysis	CACNA1S and SCN4A Sequencing and/or Deletion/Duplication Analysis	E87.6, G27.3
81400-81408	*See list below*	Other Epilepsy, Neuromuscular and Neurodegenerative Disorders	N/A

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

- ***CP.MP.235 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.
- ***CP.MP.234 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).
- ***CP.MP.232 Genetic Testing: Pharmacogenetics*** for coverage criteria related to genetic testing prior to the initiation of drug treatment with carbamazepine.
- ***CP.MP.229 Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders*** for coverage criteria related to genetic testing for mitochondrial disorders.
- ***CP.MP.235 Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing.
- ***CP.MP.233 Genetic Testing: Preimplantation Genetic Testing*** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***CP.MP.222 Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to epilepsy, neuromuscular, and neurodegenerative disorders not specifically discussed in this or another non-general policy.

Policy/Criteria

Known Familial Variant Analysis for Epilepsy, Neurodegenerative, and Neuromuscular Disorders

I. It is the policy of health plans affiliated with Centene Corporation© that targeted mutation analysis for a known familial variant (81403, 81326, 81337) for an epilepsy, neurodegenerative, or neuromuscular disorder is considered **medically necessary** when the member/enrollee has a close relative[1] with a known pathogenic or likely pathogenic variant causing the condition.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support targeted mutation analysis for a known familial variant (81403, 81326, 81337) for an epilepsy, neurodegenerative, or neuromuscular disorder for all other indications.

Comprehensive Neuromuscular Disorders Panel

I. It is the policy of health plans affiliated with Centene Corporation that comprehensive neuromuscular panel analysis to establish a genetic diagnosis for a neuromuscular disorder (81479, 81443) is considered **medically necessary** when meeting both of the following:

   A. The member/enrollee displays clinical features of a neuromuscular disorder;

   B. One of the following:

      1. The member/enrollee is not highly suspected to have a specific neuromuscular disorder for which single-gene analysis (e.g., *SMN1, DMD, PMP22*) would be more appropriate;

      2. The member/enrollee previously underwent single-gene analysis for a neuromuscular disorder (e.g., *SMN1, DMD, PMP22*) and the results were negative.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support comprehensive neuromuscular panel analysis to establish a genetic diagnosis for a neuromuscular disorder (81479, 81443) for all other indications.

Comprehensive Ataxia Panel

I. It is the policy of health plans affiliated with Centene Corporation that comprehensive ataxia panel analysis to establish a genetic diagnosis of an ataxia (81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 0216U, 0217U, 81479, 81443) is considered **medically necessary** when meeting both of the following:

   A. The member/enrollee displays one or more of the following clinical features of spinocerebellar ataxia:

      1. Progressive incoordination of movement and speech

      2. Wide-based, uncoordinated, unsteady gait

      3. Muscle stiffness

      4. Weakness of the eye muscles (ophthalmoplegia)

      5. Dysarthria

      6. Eye movement abnormalities (nystagmus, abnormal saccade movements);

B. Non-genetic causes of ataxia have been ruled out (e.g., alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, primary or metastatic tumors, and paraneoplastic disease associated with occult carcinoma of the ovary, breast, or lung and spinal muscular atrophy).

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support comprehensive ataxia panel analysis to establish a genetic diagnosis of an ataxia (81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 0216U, 0217U, 81479, 81443) for all other indications.

Spinal Muscular Atrophy

SMN1 Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation that *SMN1* sequencing (81336, 81405, 0236U) and/or deletion/duplication analysis (81329, 81401) to establish or confirm a diagnosis of Spinal Muscular Atrophy is considered **medically necessary** when meeting one of the following:

A. The member/enrollee has a positive newborn screen for SMA;

B. The member/enrollee; has any of the following clinical features of SMA:

1. History of motor difficulties, especially with loss of skills
2. Proximal to distal muscle weakness
3. Hypotonia
4. Areflexia/hyporeflexia
5. Tongue fasciculations
6. Hand tremor
7. Recurrent lower respiratory tract infections or severe bronchiolitis in the first few months of life
8. Evidence of motor unit disease on electromyogram

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *SMN1* sequencing (81336, 81405, 0236U) and/or deletion/duplication analysis (81329, 81401) to establish or confirm a diagnosis of Spinal Muscular Atrophy for all other indications.

SMN2 Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation that *SMN2* deletion/duplication analysis (81401) is considered **medically necessary** when the member/enrollee has a diagnosis of spinal muscular atrophy.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *SMN2* deletion/duplication analysis (81401) for all other indications.

Epilepsy

Epilepsy Multigene Panel

I. It is the policy of health plans affiliated with Centene Corporation that the use of an epilepsy multigene panel (81419) is considered **medically necessary** when meeting all of the following:

A. The member/enrollee has infantile- or early-childhood-onset epilepsy* (onset of seizures before the age of 5);

B. The member/enrollee does not have any metabolic or brain structural abnormalities that predispose to epilepsy;

C. The panel includes, at a minimum, all of the following genes: *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*.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support the use of an epilepsy multigene panel (81419) for all other indications.

* Some examples of infantile- and early-childhood-onset epilepsy syndromes in which epilepsy is the core clinical symptom include: Dravet syndrome, early infantile epileptic encephalopathy, generalized epilepsy with febrile seizures plus, epilepsy and intellectual disability limited to females, nocturnal frontal lobe epilepsy.

Alzheimer Disease

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

I. It is the policy of health plans affiliated with Centene Corporation that *PSEN1* (81405, S3855), *PSEN2* (81406), and/or *APP* (81406) sequencing and/or deletion/duplication analysis (S3855, 81405, 81406) or multigene panel (S3855, 81405, 81406) to establish a diagnosis or determine future risk to develop early-onset Alzheimer disease* is considered **medically necessary** when meeting one of the following:

A. The member/enrollee is 18 years of age and asymptomatic**, with a first[1a]- or second-degree[1b] relative with a known early-onset Alzheimer disease-causing mutation in *PSEN1*, *PSEN2*, or *APP*;

B. The member/enrollee is symptomatic, with a diagnosis of dementia at ≤65 years of age, and one of the following:

a) The member/enrollee has a first[1a]- or second-degree[1b] relative diagnosed with dementia;

b) An unknown family history (e.g., adoption).

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *PSEN1* (81405, S3855), *PSEN2* (81406), and/or *APP* (81406) sequencing and/or deletion/duplication analysis (S3855, 81405, 81406) to establish the diagnosis or determine future risk to develop early-onset Alzheimer disease* for all other indications.

APOE, TREM2 and Others Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support genetic testing to establish a diagnosis or determine future risk to develop Alzheimer disease via other genes, including but not limited to, *APOE* (81401 S3852) or *TREM2* (81479).

* Early-onset Alzheimer disease is defined as Alzheimer disease occurring in an individual under age 65.
** Predictive testing should only be performed in the setting and context of thorough pre- and post-test counseling

Amyotrophic Lateral Sclerosis (ALS)
ALS Multigene Panel Analysis

I. It is the policy of health plans affiliated with Centene Corporation that multigene panel analysis to establish a genetic etiology of amyotrophic lateral sclerosis (ALS) (81404, 81405, 81406, 81479, S3800) is considered **medically necessary** when meeting all of the following:

    A. The member/enrollee is 18 years of age or older;

    B. The member/enrollee displays all of the following clinical features of ALS:

        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;

    C. The panel includes, at a minimum, the following genes: *C9orf72*, *SOD1*, *FUS*, and *TARDBP*.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support multigene panel analysis to establish a genetic etiology of amyotrophic lateral sclerosis (ALS) (81404, 81405, 81406, 81479, S3800) for all other indications.

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

I. It is the policy of health plans affiliated with Centene Corporation that *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) is considered **medically necessary** when meeting one of the following:

A. The member/enrollee is a male and meets one of the following:

1. All of the following clinical findings of DMD:

a) Progressive symmetric muscular weakness - proximal greater than distal, often with calf hypertrophy (enlargement)

b) Symptoms presenting before age five years

c) Wheelchair dependency before age 13 years

d) Serum creatine kinase concentration more than 10 times the normal levels;

2. Any of the following clinical findings of BMD:

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

b) Activity-induced cramping

c) Flexion contractures of the elbows

d) Wheelchair dependency (after age 16 years)

e) Preservation of neck flexor muscle strength;

3. The member/enrollee is asymptomatic and one of the following:

a) Has a biological sibling[1a] with a clinical and/or molecular diagnosis of Duchenne or Becker muscular dystrophy;

b) Has a biological mother that is an obligate carrier for Duchenne or Becker muscular dystrophy;

B. The member/enrollee is a female and has a first[1a]- or second-degree[1b] relative with a clinical diagnosis of Duchenne or Becker muscular dystrophy.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *DMD* sequencing and/or deletion/duplication analysis (81161, 81408, 0218U) to establish a diagnosis of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) for all other indications.

Facioscapulohumeral Muscular Dystrophy (FSHD)
FSHMD1A Deletion/Duplication or Haplotype Analysis, and/or SMCHD1 and DNMT3B Sequencing and/or Deletion/Duplication Analysis or Multigene Panel

I. It is the policy of health plans affiliated with Centene Corporation that *FSHMD1A* deletion/duplication or haplotype analysis (81404), and/or *SMCHD1* (81404, 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 **medically necessary** when:

A. The member/enrollee displays any of the following clinical features of FSHD:

1. Weakness (which is often asymmetric) that predominantly involves the facial, scapular stabilizer, or foot dorsiflexor muscles without associated ocular or bulbar muscle weakness

2. Progression of weakness after pregnancy

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

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *FSHMD1A* deletion/duplication or haplotype analysis (81404), and/or *SMCHD1* (81404, 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 for all other indications.

<u>Friedreich's Ataxia</u>
FXN Repeat Analysis

I. It is the policy of health plans affiliated with Centene Corporation that *FXN* repeat analysis (81284, 81285, 81289, 81401) or sequencing analysis (81286, 81404, 0233U) to establish or confirm a diagnosis of Friedreich's Ataxia is considered **medically necessary** when meeting one of the following:

A. The member/enrollee is asymptomatic and has a biological sibling diagnosed with Friedreich's ataxia;

B. The member/enrollee has been diagnosed with cerebellar ataxia non-genetic causes for the ataxia have been ruled out (e.g., alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, tumors).

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not supoprt *FXN* repeat analysis (81284, 81285, 81289, 81401) and sequencing analysis (81286, 81404, 0233U) to establish or confirm a diagnosis of Friedreich's Ataxia for all other indications.

<u>Huntington Disease</u>
HTT Repeat Analysis

I. It is the policy of health plans affiliated with Centene Corporation that genetic testing of *HTT* repeat analysis to establish a diagnosis or for predictive testing of Huntington's

disease (HD) (81271, 81274, 81401) is considered **medically necessary** when meeting one of the following:

A. The member/enrollee displays at least two of the following clinical features of Huntington disease:

1. Progressive motor disability featuring chorea and gait disturbance
2. Mental disturbances including any of the following:
   a) Cognitive decline
   b) Changes in personality
   c) Depression;

B. The member/enrollee is presymptomatic/asymptomatic, is undergoing predictive testing*, and meets one of the following:

1. The member/enrollee has a close relative[1] with CAG trinucleotide repeat expansion of 27 or more in *HTT;*
2. The member/enrollee has a first-degree relative[1a] with a clinical diagnosis of HD without prior genetic testing.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support genetic testing of *HTT* repeat analysis to establish a diagnosis or for predictive testing of Huntington's disease (HD) (81271, 81274, 81401) 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 (e.g. Charcot-Marie-Tooth Disease and Hereditary Neuropathy with Liability to Pressure Palsies)

PMP22 Sequencing and/or Deletion/Duplication or Multigene Panel

I. It is the policy of health plans affiliated with Centene Corporation that PMP22 Sequencing and/or Deletion/Duplication analysis (81324, 81325) or multigene panel analysis to establish a genetic diagnosis of an inherited peripheral neuropathy (81403, 81404, 81405, 81406, 81448, 81479) is considered **medically necessary** when meeting one of the following:

A. The member/enrollee displays one or more of the following clinical features of an inherited motor or sensory peripheral neuropathy:

1. Distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity
2. Pes cavus foot deformity

3. Enlarged nerves
4. Weak ankle dorsiflexion
5. Depressed tendon reflexes
6. Repeated focal pressure neuropathies such as carpal tunnel syndrome and peroneal palsy with foot drop

B. The member/enrollee is asymptomatic and has a close relative[1] diagnosed with an inherited peripheral neuropathy whose genetic status is unavailable.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support PMP22 Sequencing and/or Deletion/Duplication analysis (81324, 81325) or multigene panel analysis to establish a genetic diagnosis of an inherited peripheral neuropathy (81403, 81404, 81405, 81406, 81448, 81479) for all other indications.

Limb-Girdle Muscular Dystrophy (LGMD)
Limb-girdle Muscular Dystrophy Multigene Panel
Congenital Heart Malformation Panels

I. Multigene panel analysis to establish a diagnosis of limb-girdle muscular dystrophy (81400, 81404, 81405, 81406, 81408, 81479) is considered **medically necessary** when meeting one of the following:

A. The member/enrollee displays any of the following clinical features of limb-girdle muscular dystrophy:

1. Gradually progressive muscle weakness involving predominantly the proximal arms and legs, with normal sensory exam (distal muscles are involved, but usually to a lesser extent)
2. Elevated creatine kinase level;

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

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support multigene panel analysis to establish a diagnosis of limb-girdle muscular dystrophy (81400, 81404, 81405, 81406, 81408, 81479) for all other indications.

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

I. It is the policy of health plans affiliated with Centene Corporation that *DMPK* repeat analysis (81234, 81239, 81401, 81404, S3853) and/or *CNBP* (*ZNF9*) repeat analysis (81187, 81401, S3853) to establish a diagnosis of myotonic dystrophy is considered **medically necessary** when meeting one of the following:

A. The member/enrollee meets either of the following:

1. Neonate (< 4 weeks of age) with two or more of the following:

a) Hypotonia

b) Facial muscle weakness

c) Generalized weakness

d) Positional malformations, including clubfoot

e) Respiratory insufficiency;

2. Any age and displays any of the following clinical features of myotonic dystrophy:

a) Muscle weakness, especially of the distal leg, hand, neck, and face

b) Myotonia, which often manifests as the inability to quickly release a hand grip (grip myotonia)

c) Posterior subcapsular cataracts

d) Cardiac conduction defects or progressive cardiomyopathy

e) Insulin sensitivity

f) Hypogammaglobulinemia;

B. The member/enrollee is asymptomatic and meets both of the following:

1. 18 years of age or older

2. The member/enrollee has a first-degree relative[1a] with Myotonic dystrophy type 1 or 2.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *DMPK* repeat analysis (81234, 81239, 81401, 81404, S3853) and *CNBP* (*ZNF9*) repeat analysis (81187, 81401, S3853) to establish a diagnosis of myotonic dystrophy for all other indications.

Hereditary Dystonia

Hereditary Dystonia Multigene Panel

I. It is the policy of health plans affiliated with Centene Corporation that multigene panel analysis to establish a genetic diagnosis of hereditary dystonia (81400, 81404, 81405, 81406, 81443) is considered **medically necessary** when the member/enrollee has all of the following clinical features of a hereditary dystonia:

A. Sustained, intermittent muscle contractions

B. Abnormal or repetitive movements and/or postures

C. The dystonia is initiated or worsened by voluntary action

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support multigene panel analysis to establish a genetic diagnosis of hereditary dystonia (81400, 81404, 81405, 81406, 81443) for all other indications.

Parkinson Disease

GBA, *LRRK2*, *SNCA*, and *VPS35* Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation that *GBA* (81479), *LRRK2* (81402, 81408), *SNCA* (81479) and *VPS35* (81479) sequencing and/or deletion/duplication analysis to establish a genetic diagnosis of Parkinson disease is considered **medically necessary** when meeting both of the following:

A. The member/enrollee has a diagnosis of Parkinson disease

B. The member/enrollee has two or more first-degree[1a] or second-degree[1b] relatives who have been diagnosed with Parkinson disease.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *GBA* (81479), *LRRK2* (81402, 81408), *SNCA* (81479) and *VPS35* (81479) sequencing and/or deletion/duplication analysis to establish a genetic diagnosis of Parkinson disease for all other indications.

III. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support all other genetic testing to establish a genetic diagnosis of Parkinson disease.

Hereditary Spastic Paraplegia

Hereditary Spastic Paraplegia Multigene Panel

I. It is the policy of health plans affiliated with Centene Corporation that multigene panel analysis to establish a genetic diagnosis of hereditary spastic paraplegia (81405, 81406, 81407, 81448, 81479) is considered **medically necessary** when:

A. The member/enrollee has a close relative[1] with a known or suspected diagnosis of spastic paraplegia and one of the following:

1. The member/enrollee has progressive and mostly symmetric lower-extremity weakness and spasticity and one of the following:

a) Onset of symptoms occurred before 10 years of age

b) The member/enrollee has mild intellectual disability with learning difficulties in childhood

c) The member/enrollee has progressive cognitive decline with onset in the first to third decade

d) The member/enrollee has axonal, motor, or sensorimotor peripheral neuropathy;

2. The member/enrollee has insidiously progressive bilateral leg stiffness affecting gait with or without spasticity at rest and mild proximal weakness and:

a) Neurologic examination demonstrates one of the following:

(1) Corticospinal tract deficits affecting both legs

(2) Cerebellar atrophy (MRI) or white matter changes as detected by diffusion tensor imaging in the frontal lobes, the corticospinal tracts, and the brain stem

(3) A pure phenotype of spastic paraplegia (may include hyperreflexia, extensor plantar responses, and mildly impaired vibration sensation in the distal legs)

(4) A complicated phenotype of spastic paraplegia (may include optic neuropathy, progressive external ophthalmoplegia/ptosis slowed speech, swallowing difficulties, palatal tremor, subtle cognitive impairment, urinary urgency, ataxia, nystagmus, strabismus, decreased hearing, scoliosis, pes cavus, motor and sensory neuropathy, and amyotrophy)

3. The member/enrollee has progressive pure phenotype of spastic paraplegia and urinary urgency with onset before the age of 40 years old.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support multigene panel analysis to establish a genetic diagnosis of hereditary spastic paraplegia (81405, 81406, 81407, 81448, 81479) for all other indications.

<u>Congenital Myasthenic Syndromes</u>

Congenital Myasthenic Syndromes Multigene Panel

I. It is the policy of health plans affiliated with Centene Corporation that multigene panel analysis to establish a genetic diagnosis of congenital myasthenic syndromes (81479) is considered **medically necessary** when meeting all of the following:

A. The member/enrollee has a history of fatigable weakness involving ocular, bulbar, and limb muscles with onset at or shortly after birth or in early childhood

B. A decremental EMG response of the compound muscle action potential (CMAP) on low-frequency (2-3 Hz) stimulation

C. A positive response to acetylcholinesterase (AchE) inhibitors

D. Absence of anti-acetylcholine receptor (anti-AChR) and anti-MuSK antibodies in the serum

E. Lack of improvement of clinical symptoms with immunosuppressive therapy

F. Absence of major pathology in a skeletal muscle biopsy specimen despite considerable muscle weakness.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support multigene panel analysis to establish a genetic diagnosis of congenital myasthenic syndromes (81479) for all other indications.

Myotonia Congenita

CLCN1 Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation that *CLCN1* sequencing and/or deletion/duplication analysis (81406) to establish a genetic diagnosis of myotonia congenita is considered **medically necessary** when meeting all the following:

A. The member/enrollee has episodes of muscle stiffness (myotonia*) or cramps beginning in early childhood which is alleviated by brief exercise

B. Myotonic contraction is elicited by percussion of muscles

C. Serum creatine kinase concentration that may be slightly elevated (≤3-4x the upper limits of normal)

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

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *CLCN1* sequencing and/or deletion/duplication analysis (81406) to establish a genetic diagnosis of myotonia congenita for all other indications.

*Myotonia is defined as impaired relaxation of skeletal muscle after voluntary contraction.

Hypokalemic Periodic Paralysis

CACNA1S and *SCN4A* Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation that *CACNA1S* and *SCN4A* sequencing and/or deletion/duplication analysis (81406, 81479) to establish a genetic diagnosis of periodic paralysis is considered **medically necessary** when:

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

1. The member/enrollee has had two or more attacks of muscle weakness with documented serum potassium <3.5 mEq/L
2. The member/enrollee has had one attack of muscle weakness and has a close relative[1] who has had one attack of muscle weakness in with documented serum potassium <3.5 mEq/L
3. The member/enrollee has three or more of the following features:
    a) Onset of symptoms in the first or second decade
    b) Muscle weakness involving ≥1 limbs lasting longer than two hours
    c) The presence of triggers (previous carbohydrate rich meal, symptom onset during rest after exercise, stress)
    d) Improvement in symptoms with potassium intake
    e) A family history of a clinical or genetic diagnosis of hypokalemic periodic paralysis in a close relative[1]
    f) Positive long exercise test.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *CACNA1S* and *SCN4A* sequencing and/or deletion/duplication analysis (81406, 81479) to establish a genetic diagnosis of periodic paralysis for all other indications.

Other Epilepsy, Neuromuscular, And Neurodegenerative Disorders

The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.

I. It is the policy of health plans affiliated with Centene Corporation that genetic testing to establish or confirm one of the following epilepsy, neuromuscular, and neurodegenerative conditions to guide management is considered **medically necessary** when the member/enrollee demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II below):

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

II. It is the policy of health plans affiliated with Centene Corporation that genetic testing to establish or confirm the diagnosis of all other epilepsy, neurodegenerative, and neuromuscular disorders not specifically discussed within this or another medical policy

will be evaluated by the criteria outlined in *General Approach to Genetic Testing* (see policy for coverage criteria).

*Clinical features for a specific disorder may be outlined in resources such as GeneReviews, OMIM, National Library of Medicine, Genetics Home Reference, or other scholarly source.

Notes and 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

Background

American Academy of Neurology

Genetic Testing for Inherited Peripheral Neuropathies

The American Academy of Neurology and 2 other specialty societies (2009) published an evidence-based, tiered approach for the evaluation of distal symmetric polyneuropathy and suspected hereditary neuropathies and recommended that genetic testing is established as useful for the accurate diagnosis and classification of hereditary neuropathies.

Genetic Testing for Epilepsy

The American Academy of Neurology and Child Neurology Society published joint guidelines (2006) which were reviewed and reaffirmed in 2016. The guidelines stated that there is insufficient evidence to support or refute whether genetic testing should be done routinely.

Genetic Testing for Facioscapulohumeral Muscular Dystrophy

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.

Genetic Testing for Limb-Girdle Muscular Dystrophy

The American Academy of Neurology and the American Association of Neuromuscular and Electrodiagnostic Medicine (2014) issued evidenced-based guidelines for the diagnosis and treatment of limb-girdle and distal dystrophies. These guidelines recommend that "For patients with suspected muscular dystrophy, clinicians should use a clinical approach to guide genetic diagnosis based on the clinical phenotype, including the pattern of muscle involvement, inheritance pattern, age at onset, and associated manifestations (e.g., early contractures, cardiac or respiratory involvement) (Level B). In patients with suspected muscular dystrophy in whom

initial clinically directed genetic testing does not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole-genome screening, or next-generation sequencing to identify the genetic abnormality (Level C)."

Genetic Testing for Alzheimer Disease

The American Academy of Neurology (2001) made the guideline recommendations that routine use of *APOE* genotyping in patients with suspected AD is not recommended.

American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM)

The AANEM developed a position statement regarding the clinical usefulness of genetic testing in the diagnosis of neuromuscular disease (2016) generally supporting the use of genetic testing in the diagnosis of neuromuscular disorders, which made the following summary statement:

> "The AANEM believes that genetic testing and arriving at a specific molecular diagnosis is critical to providing high quality care to NM patients. Many recommendations and guidelines exist to direct the rational selection of appropriate genetic testing. The cost of testing should not be a deterrent, since there are important clinical, safety, psychosocial, and research benefits to genetic testing in NM disease."

American Academy of Family Physicians

Genetic Testing for Inherited Peripheral Neuropathies

The American Academy of Family Physicians (2010) recommended genetic testing for a patient with suspected peripheral neuropathy, if basic blood tests are negative, electrodiagnostic studies suggest an axonal etiology and diseases such as diabetes, toxic medications, thyroid disease, and vasculitides can be ruled out.

American College of Medical Genetics and National Society of Genetic Counselors

Genetic Testing for Alzheimer Disease

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

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

The American College of Medical Genetics and Genomics has listed genetic testing for apolipoprotein E (*APOE*) alleles as 1 of 5 recommendations in the Choosing Wisely initiative. The recommendation is "Don't order APOE genetic testing as a predictive test for Alzheimer disease." The stated rationale is that *APOE* is a susceptibility gene for late-onset Alzheimer disease (AD), the most common cause of dementia: "The presence of an ε4 allele is neither necessary nor sufficient to cause AD. The relative risk conferred by the ε4 allele is confounded by the presence of other risk alleles, gender, environment and possibly ethnicity, and the APOE genotyping for AD risk prediction has limited clinical utility and poor predictive value."

American College of Medical Genetics

Genetic Testing for Hereditary Ataxias

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

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

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

National Society of Genetic Counselors

The National Society of Genetic Counselors updated a position statement (2017) regarding the genetic testing of minors for adult-onset conditions, stating the following:

> "[NSGC] 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."

International League Against Epilepsy

Genetic Testing for Epilepsy

In 2015, the International League Against Epilepsy issued a report with recommendations on the management of infantile seizures, which included the following related to genetic testing in epilepsy:

- Genetic screening should not be undertaken at primary or secondary level care (expert opinion).
- Standard care should permit genetic counseling by trained personnel at all levels of care (expert opinion).
- Genetic evaluation for Dravet syndrome, and other infantile-onset epileptic encephalopathies, should be available in tertiary care (weak evidence, level C recommendation).

American Academy of Pediatrics (AAP)

Genetic Testing for Duchenne and Becker Muscular Dystrophy

The AAP (2005, reaffirmed in 2008) published the following recommendations for cardiac care in carriers of DMD or BMD:

- Carriers of DMD or BMD should be made aware of the risk of developing cardiomyopathy and educated about the signs and symptoms of heart failure.

- Carriers of DMD or BMD should be referred for evaluation by a cardiac specialist with experience in the treatment of heart failure and/or neuromuscular disorders. Patients should undergo initial complete cardiac evaluation in late adolescence or early adulthood or at the onset of cardiac signs and symptoms, if these signs or symptoms appear earlier.
- Carriers should be screened with a complete cardiac evaluation at a minimum of every 5 years starting at 25 to 30 years of age.
- Treatment of cardiac disease is similar to that outlined for boys with DMD or BMD.

DMD Care Considerations Working Group

Genetic Testing for Duchenne and Becker Muscular Dystrophy

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."

Myotonic Dystrophy Foundation

Genetic Testing for Myotonic Dystrophy Type 1

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."

Genetic Testing for Myotonic Dystrophy Type 2

15 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."

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2021, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy Implemented	02/22	02/22

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