Genetic Testing for Neurological Disorders

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➲ Instructions for Use

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Related Commercial/Individual Exchange Policies

- Chromosome Microarray Testing (Non-Oncology Conditions)
- Genetic Testing for Cardiac Disease
- Whole Exome and Whole Genome Sequencing (Non-Oncology Conditions)

Community Plan Policy

- Genetic Testing for Neuromuscular Disorders

Medicare Advantage Policy

- Molecular Pathology/Molecular Diagnostics/ Genetic Testing

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

Multi-gene Targeted Panel testing (five or more genes) for neurological disorders is proven and medically necessary when all of the following criteria are met:

- The individual to be tested displays signs or symptoms of a heritable neurological disorder and the results are expected to directly impact medical management of that disorder; and
- The test is ordered by or in consultation with a medical geneticist, developmental pediatrician, or adult or pediatric neuromuscular or neurogenetics specialist; and
- The test is intended to establish a genetic cause for any one of the following:
  - Congenital or Metabolic Myopathy
  - Ataxia
  - Peripheral neuropathy
  - Hereditary spastic paraplegia
  - Muscular dystrophy

Comprehensive Panel tests intended to evaluate multiple genes associated with multiple categories of clinically distinct neurological disorders are unproven and not medically necessary due to insufficient evidence of efficacy.

Note: Whole Exome and Whole Genome Sequencing are addressed in the Medical Policy titled Whole Exome and Whole Genome Sequencing (Non-Oncology Conditions).

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled Medical Records Documentation Used for Reviews.

Definitions

Ataxia: A condition of the nervous system that causes loss of control of muscle movement and coordination. Ataxia can be a symptom of another condition or can happen on its own (National Institute of Neurological Disorders and Stroke, 2025).

Comprehensive Panel: An assay that simultaneously tests more than one gene associated with a variety of conditions, symptoms, or non-overlapping clinical presentations (Rehder et al., 2021).

Congenital Myopathy: An abnormality affecting muscle development, typically manifesting at birth or during early infancy. The clinical presentation may include muscle weakness, hypotonia, and respiratory distress. Central core disease, minimulticore disease, centronuclear myopathy, and nemaline myopathy are examples of Congenital Myopathies (Zhang et al., 2024).

Metabolic Myopathy: An abnormality resulting from certain inborn errors of metabolism, such as the glycogen storage diseases and the fatty acid metabolism defects. The clinical presentation of a Metabolic Myopathy may include muscle cramps, exercise intolerance, and progressive weakness in the trunk and extremities (Manta et al., 2021).

Targeted Panel: A curated assay that simultaneously tests more than one gene associated with a condition. A Targeted Panel may consist of multiple genes that are associated with one specific genetic condition or multiple genes that are associated with a symptom or non-specific clinical presentation (Rehder et al., 2021).

Whole Exome Sequencing (WES)*:* About 1% of a person's DNA makes protein. These protein-making sections are called exons. All the exons together are called the exome. WES is a DNA analysis technique that looks at all of the exons in a person's DNA at one time rather than gene by gene (MedlinePlus, 2021).

Whole Genome Sequencing (WGS)*:* WGS determines the sequence of all the nucleotides in a person's entire DNA including the protein-making (coding) as well as non-coding DNA elements (MedlinePlus, 2021).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
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
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

Description of Services

Neurological disorders are conditions that affect how the nervous system functions. Genetic testing for neurological disorders can range from targeted testing of a known family variant to multi-gene panels to broader testing such as Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS). Results of genetic testing may assist individuals and healthcare providers with determining a diagnosis and/or prognosis and identification of appropriate clinical interventions (Ghaoui et al., 2015).

Neurological disorders include the categories of neurodegenerative conditions, neuromuscular conditions, and other conditions affecting the brain, spine, or peripheral nerves. There are hundreds of neurological disorders, some of which have genetic causes. Some examples of heritable neurological disorders are the muscular dystrophies (including collagenopathies such as Ullrich congenital muscular dystrophy and Bethlem myopathy, merosin-deficient congenital muscular dystrophy, and the dystroglycanopathies), the spinocerebellar Ataxias (SCAs), Charcot-Marie-Tooth (CMT) disease, hereditary sensory and autonomic neuropathy (HSAN), hereditary motor neuropathy, hereditary neuropathy with liability to pressure palsies (HNLPP), hereditary spastic paraplegia (HSP), and certain inborn errors of metabolism. There can be overlap in the genes responsible for multiple neurological disorders, such as those implicated in both hereditary Ataxia and HSP (Fereshtehnejad et al., 2023). Over 500 genes have been associated with neuromuscular disorders (NMDs) (Antoniadi et al., 2015, Efthymiou et al., 2016).

This policy addresses multi-gene genetic test panels with five or more genes for neurological disorders.

Clinical Evidence

Current evidence does not support the clinical utility of Comprehensive Panel testing for individuals with signs or symptoms of heritable neurological disorders. Studies consistently show that an individual's phenotype typically correlates with variants in genes already known to be associated with that presentation. This genotype-phenotype relationship supports the use of Targeted Panels for accurate diagnosis and informed clinical decision-making. In contrast, Comprehensive Panels assess genes unrelated to the individual's phenotype and lack supporting clinical evidence at this time.

Alhammad et al. (2024) conducted a retrospective cohort study to characterize the clinical and genetic spectrum of hereditary myopathies in an adult Saudi population. The study reviewed medical records of 87 patients from 78 families evaluated at a tertiary hospital in Riyadh between January 2018 and December 2022. Testing methodologies included whole exome sequencing (WES), whole genome sequencing (WGS), a next-generation sequencing (NGS) neuromuscular panel, and single gene or targeted analysis, chosen at the discretion of the treating physician. The most common clinical diagnosis was limb-girdle muscular dystrophy (LGMD), accounting for 29% of cases. Among 22 patients with LGMD who underwent genetic testing, a molecular diagnosis was achieved in 15 (68%). The most frequently identified genetic subtypes of LGMD were dysferlinopathy (27%), *FKRP*-related LGMD (20%), sarcoglycanopathy (20%), lamin A/C-related myopathy (13%), and calpain-3 myopathy (13%). A subset of 26 patients from the study cohort were found to have pathogenic or likely pathogenic variants through genetic testing. Among these 26 patients, genetic testing methods included WES (42%), NGS panel (31%), and targeted single-gene analysis (27%). The diagnostic sensitivity varied by method: 100% for targeted single-gene analysis and *D4Z4* repeat array testing, 88% for *DMPK* repeat expansion analysis, 42% for the NGS panel, and 46% for WES. The authors concluded that the distribution of hereditary myopathies in this cohort was consistent with global patterns and emphasized the importance of access to advanced molecular diagnostics, particularly for conditions such as facioscapulohumeral muscular dystrophy and mitochondrial myopathies. The study's limitations include its retrospective cohort design and its single-center setting, at which there was restricted availability of immunohistochemical stains and mitochondrial genome sequencing, potentially overestimating the diagnostic yield of the genetic analysis reported here. While the study population is represented as 87 patients, 24 of those patients did not undergo genetic testing due to unavailability or unspecified reasons.

Ebert et al. (2024) retrospectively examined the clinical usefulness and detection rate of genetic testing for individuals with suspected neuromuscular disorders (NMDs) at a single, large neuromuscular center. The authors obtained results for all patients who had multi-gene panel testing for NMDs (defined as neuropathy, myopathy or nondystrophic myotonia, neuromuscular junction disease, or motor neuron disease) with one of two comprehensive panels (230-gene neuromuscular disorders panel or 111-gene neuropathies panel) through a single genetic testing laboratory (n = 192), performing a chart review to determine whether genetic testing confirmed a specific neuromuscular diagnosis, including cases where a variant of uncertain significance (VUS) was identified. They found that the test identified a pathogenic mutation, a VUS, or both in 77.1% of patients, conferring a definitive diagnosis in 35.9%. The most common indication for testing was suspected neuropathy (53.3%), while myopathy was the indication with the highest diagnostic yield (48.7%).

The main limitations of this study are its single-center design, which indicates the findings may not be generalizable, and the exclusion of specimens sent to other laboratories during the study period. Furthermore, this study was limited by the choice to focus exclusively on multi-gene panel testing. Overall diagnostic yield might improve on the results reported here if all types of genetic studies were considered. The authors asserted that their results bolster the existing evidence in support of the use of genetic testing as an aid in the diagnosis and management of NMDs.

Hu et al. (2024) conducted a retrospective observational multicenter study to characterize the clinical, pathological, and genetic features of collagen VI-related disorders (COLVI-RD) in a Chinese population. The study included 82 participants diagnosed with COLVI-RD from two tertiary neuromuscular centers between 2011 and 2023. Participants were classified into four phenotypic groups: early-severe Ullrich congenital muscular dystrophy (E-S UCMD, 4.8%), moderate-progressive UCMD (M-P UCMD, 54.9%), mild UCMD (23.2%), and Bethlem myopathy (BM, 17.1%). Clinical data, muscle biopsy results when available (n = 47), and genetic testing were analyzed. Immunofluorescence staining for collagen VI revealed complete deficiency in 10 participants, sarcolemma-specific deficiency in 25 participants, and normal expression in 9 participants. Genetic testing identified 64 pathogenic variants in COLVI-related genes in 70 participants, including 33 novel mutations. Mutations were most frequently found in *COL6A1* (n = 28), followed by *COL6A2* (n = 25) and *COL6A3* (n = 17). Missense and splicing mutations were predominant in *COL6A1* and *COL6A3*, while *COL6A2* mutations were more polymorphic and distributed across the gene. The study found that severe phenotypes were more often associated with sporadic dominant or recessive mutations, while milder phenotypes included both sporadic and autosomal dominant inheritance. The authors concluded that M-P UCMD was the most common phenotype in this cohort and that the findings expanded the clinical and genetic spectrum of COLVI-RD in the Chinese population. The authors acknowledged several limitations, including lack of standardized motor function assessments, absence of data on phenotypic features such as contractures and spinal deformities due to reliance on retrospective motor milestone data, and incomplete follow-up for some patients. Furthermore, this study claims to have identified 33 novel mutations as well as rare mechanisms such as uniparental disomy and mosaicism. These findings would benefit from replication and functional validation.

Radziwonik-Fraczyk et al. (2024) conducted a prospective cohort study to evaluate the diagnostic utility of a custom-designed NGS panel in patients with NMDs presenting with heterogeneous clinical phenotypes. The study included 52 Polish patients who underwent genetic testing using a targeted NGS panel of 89 genes. Additional testing included genotyping for myotonic dystrophy types 1 and 2 (DM1 and DM2) and multiplex ligation-dependent probe amplification (MLPA) for copy number variant (CNV) detection. A molecular diagnosis was achieved in 29 patients (55.8%) using the NGS panel alone. When combined with genotyping and MLPA, the diagnostic yield increased to 57.7% (30/52). The most frequently implicated genes were *CLCN1*, *CAPN3*, *SCN4A*, and *SGCA*. Co-occurring mutations in *CAPN3* and *CNBP* and in *DYSF* and *CNBP*, were identified in two patients, suggesting possible complex inheritance patterns. MLPA analysis confirmed a *CAPN3* exon 2–8 deletion in one patient, consistent with LGMD type R1. The study identified 27 known and 4 novel pathogenic or likely pathogenic variants, as well as VUSs. The authors concluded that combining NGS with complementary molecular techniques enhances diagnostic yield and broadens the mutational spectrum identified in NMDs. The detection of co-occurring variants in two individuals further supports the need for comprehensive genetic evaluation in this patient population. Limitations of this study include incomplete clinical data (e.g., creatine kinase levels, muscle biopsy) for some patients and lack of segregation analysis in some families due to unavailable samples. Also, functional validation for the identified VUSs was not performed. As a result, the pathogenicity of those variants remains speculative.

Roggenbuck et al. (2024) conducted a retrospective cohort study to assess the diagnostic and clinical utility of NGS-based multigene panel testing in patients with peripheral neuropathy. The study included 6849 adult participants who underwent clinician-ordered testing using panels ranging from 66 to 111 genes, incorporating both NGS and intragenic deletion/duplication analysis. A molecular diagnosis was identified in 8.4% (573/6,849) of participants. The majority of diagnoses (73.8%) were attributed to five genes: *PMP22*, *MFN2*, *GJB1*, *MPZ*, and *TTR*. Among those with a molecular diagnosis, 69.5% (398/573) had findings considered clinically actionable. The study also found that 39.3% of molecular diagnoses and 28.4% of actionable findings would have been missed if testing had been limited to the four genes typically evaluated under older clinical guidelines. The authors concluded that comprehensive multigene panel testing significantly improves diagnostic yield and clinical utility in patients with peripheral neuropathy and supports broader genetic testing guidelines. Limitations of the study include reliance on clinician-provided data and incomplete clinical histories for some patients, as well as the exclusion from the panel of some relatively common neuropathy-associated genes. Multiple authors disclosed employment by and stock ownership in Invitae Corporation, the commercial laboratory where testing was performed.

Çavdarlı et al. (2023) retrospectively evaluated the diagnostic rate of a 47-gene NGS-based panel to identify genetic variants in a Turkish cohort of 146 participants (ages 6 months to 67 years) suspected to have a genetic NMD based on clinical examination, laboratory findings, and imaging. Individuals who had been diagnosed previously with dystrophinopathy based on genetic evaluation of dystrophin by MLPA were excluded. The genes included in the NGS

panel targeted variants related to muscular dystrophy and myopathies that have been suggested in the literature for first-tier testing. Based on the study results, 67 participants were found to have a genetic basis for their disorder, correlating to a diagnostic yield of 46%. Twenty-three genes showed variants associated with NMDs: *CAPN3, DYSF, DMD*, *SGCA*, *TTN*, *LAMA2*, *LMNA*, *SGCB*, *COL6A1*, *DES*, *CAV3*, *FKRP*, *FKTN*, *ANO5*, *COL6A2*, *CLCN1*, *GNE*, *POMGNT1*, *POMGNT2*, *POMT2*, *SYNE1*, *TCAP*, and *FLNC*. Novel variants were identified in 16 genes. Indeterminate results were found in 27 participants, including participants with a VUS, participants heterozygous for an autosomal recessive disease, and participants found to have a variant in two different genes. The authors asserted that targeted NGS is a viable option for molecular diagnosis of NMDs such as muscular dystrophy and could reduce utilization of WES.

Ceylan et al. (2023) examined the impact of targeted NGS panels on the molecular diagnosis of CMT disease in standard clinical practice and retrospectively demonstrated the importance and limitations of NGS in the diagnosis of CMT disease. Molecular techniques including MLPA, NGS, and WES were used to identify variants related to CMT disease. After molecular evaluation with MLPA, 25 of 64 participants with suspected CMT disease (39%) were positively diagnosed. Duplication in *PMP22* was seen in 14 participants. *PMP22* deletion was seen in 11 participants. Fifty participants had NGS with targeted gene panels specific to CMT disease. Of those, 36% had pathogenic or likely pathogenic variants. Lastly, five individuals with normal NGS results underwent WES. Diagnostic yield for those who had WES was 80%. The authors determined that in this study, a targeted NGS panel was diagnostic in approximately one-third of participants after ruling-out *PMP22* deletion/duplication. They advocated for an algorithmic molecular approach to genetic evaluation, along with genetic counseling and pedigree analysis, as well as further study to uncover additional information related to the etiology of CMT disease.

Fereshtehnejad et al. (2023) conducted a systematic review and individual participant data (IPD) meta-analysis to investigate genotype-phenotype associations in hereditary spastic paraplegia (HSP) with a focus on movement disorders. The study included 1423 genetically confirmed HSP cases from 202 eligible studies published between 1990 and June 2018, of which 767 participants had movement disorders (HSP-MD) and 646 did not (HSP-nMD). The study population included participants with a wide range of spastic paraplegia genotypes, with spastic paraplegia 11 (27.7%) and spastic paraplegia 7 (18.1%) being the most common. The HSP-MD group had a significantly older age of onset (20.5 ±16.0 years) compared to the HSP-nMD group (17.1 ±14.2 years, $p < 0.001$), and a lower frequency of autosomal dominant inheritance (7.6% vs. 30.1%, $p < 0.001$). Ataxia was the most common movement disorder (82.1%), followed by gait/posture problems (71.3%), and action tremor (18.4%). Spastic paraplegia 7 was most frequently associated with ataxia, while spastic paraplegia 11 was most commonly linked to parkinsonism, dystonia, and cognitive impairment. Key findings included significant phenotypic differences between spastic paraplegia 7 and spastic paraplegia 11 within the HSP-MD group. Spastic paraplegia 7 was associated with later onset, ataxia, extraocular movement disturbances, and seizures. In contrast, spastic paraplegia 11 was more frequently associated with consanguinity, parkinsonism, dystonia, peripheral neuropathy, cognitive impairment, and mood disturbances. The authors concluded that this IPD-level meta-analysis provides the most comprehensive data to date on genotype–phenotype associations in HSP-MD. The findings offer clinically relevant diagnostic cues, particularly in resource-limited settings where genetic testing may be unavailable or inconclusive. Strengths of the study include the use of IPD meta-analysis, which allowed for detailed statistical comparisons and inclusion of rare genotypes typically excluded from conventional meta-analyses. Limitations include potential underrepresentation of HSP-nMD cases due to the search strategy, the exclusion of studies published after 2018, and challenges with missing or non-standardized data due to inconsistent clinical assessment and reporting across studies. Furthermore, the prevalence of rare phenotypes and genotypes may be overestimated due to reliance on published case reports that are more likely to report unusual or complex cases.

Rosenberg et al. (2023) retrospectively evaluated genetic testing practices through chart review, including genetic test selection, genes analyzed, and diagnostic results for 155 adults and children seen in a NMD clinic over a 3-year period. The primary objective was to improve genetic testing decisions and counseling for individuals with NMDs, since an inaccurate or delayed diagnosis can negatively impact medical treatment. The authors focused on patients with elevated creatine phosphokinase (CPK) levels and muscle weakness, since these are the most common findings associated with a referral to the NMD clinic. In total, 26 separate genetic tests were used, with diagnostic yields ranging from 0% to 66%. Over half of the patients had a comprehensive neuromuscular panel which included 110 to 211 genes that are known to be associated with muscular dystrophies, inherited myopathies, and congenital myasthenic syndromes. Overall, 262 individual tests were ordered (average of 1.7 tests per patient) and 21% of patients received a genetic diagnosis. The clinical finding most associated with a diagnostic result was elevated CPK with or without muscle weakness. All patients diagnosed with Duchenne, Emery-Dreifuss, limb-girdle, or Becker muscular dystrophy had an elevated CPK level, as did patients with any of several congenital myopathies. Additionally, all patients who were diagnosed with a myopathy had muscle weakness, as did half of patients diagnosed with a muscular dystrophy, The researchers concluded that the presence of elevated CPK, muscle weakness, or both, should prompt careful clinical assessment for these disorders and consideration of genetic testing. Study limitations included small sample size, limited data (retrospective chart review), and limited generalizability to diverse populations.

Schuermans et al. (2023) evaluated the diagnostic yield of exome sequencing and multigene panel testing in individuals with adult-onset neurologic disorders in a retrospective observational study. A cohort of 1411 individuals were selected for targeted exome sequencing-based multigene panels with genes that have been associated with six phenotypic categories: ataxia and spasticity (390 genes), leukoencephalopathy (266 genes), movement disorders (269 genes), neurodegeneration with brain iron accumulation (16 genes), paroxysmal episodic disorders (53 genes), and progressive myoclonic epilepsy (34 genes). An additional panel for 35 genes associated with amyotrophic lateral sclerosis was introduced in 2021. Genetic diagnosis was identified in 10% of the total cases, including 71 different monogenic disorders. The highest diagnostic yield was seen in individuals demonstrating ataxia or spastic paraparesis (19%) but varied based on individual phenotype. Most of the identified disorders were associated with autosomal dominant inheritance (62%). The genes that most often showed variants were *NOTCH3* (n = 13), *SPG7* (n = 11) and *RFC1* (n = 8). The authors concluded that exome sequencing -based molecular testing can successfully and efficiently diagnose adult-onset neurologic diseases. Further studies assessing other technologies such as genome sequencing are recommended.

Ando et al. (2022) sought to pinpoint genetic features in a group of Japanese individuals with Inherited peripheral neuropathy (IPN) in a large case series. Clinical information was obtained for 2695 participants. No participants with a finding of *PMP22* CNV were included in this case series. Several technologies were used for genetic evaluation including DNA microarrays, NGS-based gene panels, WES, CNV analysis, and *RFC1* repeat expansion analysis. Overall, in 909 cases of suspected IPN pathogenic or likely-pathogenic variants were detected. For participants with early-onset disease *MFN2* was the most frequent finding. *GJB1* and *MPZ* were most frequently identified as the cause of middle- and late-onset disease. *GJB1* and *MFN2* were most common in the demyelinating and axonal subtypes. Genes commonly linked to IPN were *MFN2*, *GJB1*, *MPZ,* and *MME*. CNVs in *MPZ* and *FJB1* genes and *RFC1* repeat expansions were also detected. The authors concluded that completing a comprehensive genetic evaluation for participants with suspected IPN successfully revealed genetic origins in this case series. They recommended further study focused on clinical features and the phenotype's relationship to genetic variants to continue development of best practices for assessment and early diagnosis of affected patients.

Barbosa-Gouveia et al. (2022) used NGS to evaluate 268 participants (ages 0 to 80 years) with a suspected inherited NMD in a prospective, multicenter study of the diagnostic utility of multi-gene panel testing. Three versions of a multi-gene panel were designed during the three-year study period, with progressive addition of genes to each version. Diagnostic yield of the first panel (278 genes) was 31%, while the diagnostic yield of the third panel (324 genes) increased to 40%. The mean diagnostic yield for the entire three-year study period was 36%, a value within range of reported diagnostic yields for targeted sequencing panels, clinical exome sequencing, and WES. In this study, the most common diagnoses identified were muscular dystrophies/myopathies (68.4%) and peripheral nerve diseases (22.5%). *TTN*, *RYR1,* and *ANO5* were the most common causative genes found and contributed to nearly 30% of diagnosed cases. The authors asserted that in the case of inherited NMDs, reaching a definitive diagnosis requires identification of specific variants in disease-causing genes. This is challenging due to the difficulty in designing targeted panels that maximize diagnostic yield. Additional challenges associated with NGS include the interpretation of VUSs, missing or inaccurate family histories, and the overlapping phenotypes associated with NMDs. Based on the results of this study, the authors recommended comprehensive panel testing in patients with suspected inherited NMDs. However, the study was limited by its small number of participants. Further evaluations, including high-quality studies with larger cohorts, are needed to support their suggestion.

Winckler et al. (2022) examined the diagnostic yield of a 39-gene NGS panel used as a first-tier test in the diagnosis of genetic myopathies. This cross-sectional Brazilian study included 51 cases where a genetic myopathy was suspected based on clinical findings. In this study, the diagnostic yield of the NGS panel was 52.9%. When candidate variants were included in the evaluation, the diagnostic yield increased to 60.8%. LGMD was identified in 12/25 individuals (48%) and muscular dystrophy including prominent joint contractures was diagnosed in 7/10 (70%) individuals. In 7/14 individuals (50%), a different congenital muscular disease was identified. The researchers concluded that the customized NGS panel produced high diagnostic yields when used early in the exploration of gene-related myopathies, which could translate to earlier diagnosis and potential treatments.

Benkirane et al. (2021) evaluated the efficacy of molecular diagnosis for inherited ataxia and related diseases. In this study, the researchers analyzed 366 unrelated consecutive participants with ataxia or related disorders that had not yet been diagnosed by using clinical exome-capture sequencing. Analysis was performed via an in-house pipeline combining variant ranking and CNV searches. A molecular diagnosis was established in 46% of participants. In addition, 35 mildly affected participants were found to have causative variants in genes classically associated with severe clinical presentations. The authors concluded that a significant fraction of phenotypic overlap and clinical heterogeneity is explained by hypomorphic variants that are not readily predictable.

Bowen et al. (2021) reported the clinical findings of a no-charge, sponsored NGS program called “SMA Identified”. Eligible individuals had a confirmed or suspected diagnosis of spinal muscular atrophy (SMA) or a family history of SMA. The study took place over a two-year period. A total of 2459 individuals underwent testing with an NGS-based approach looking for sequence and copy number of *SMN1* and *SMN2*. Participants were then categorized according to their test results as follows: diagnostic (two pathogenic *SMN1* variants), nearly diagnostic (*SMN1* exon-7 deletion with variant of VUS in *SMN1* or *SMN2*), indeterminate VUS (one VUS in *SMN1* or *SMN2*), carrier (heterozygous *SMN1* deletion only), or negative (no pathogenic variants or VUS in *SMN1* or *SMN2*). Analysis was completed based on clinician reported clinical findings and genetic modifiers. Diagnostic yield for diagnostic and nearly diagnostic combined was 31.3% (n = 771/2459). Clinical presentation and age of onset of symptoms were variable across individuals and dependent on *SMN2* copy number. The most common genetic etiology was homozygous deletions (96.2%). The authors concluded that use of a high-yield panel test early in evaluation of individuals who have or are at higher risk for having SMA may lead to earlier interventions in affected individuals.

Nicolau et al. (2021) provided methodology guidelines for genetic testing of muscle and neuromuscular junction disorders. The authors suggested that the individual’s phenotype guides the approach to genetic testing. Phenotypes suggesting a myopathy that requires targeted testing, such as the myotonic dystrophies, facioscapulohumeral muscular dystrophy, oculopharyngeal muscular dystrophy, the dystrophinopathies, oculopharyngodistal myopathy, and the mitochondrial myopathies, must be identified as a first step. For remaining individuals, the researchers suggest a multi-gene panel with CNVs tailored to congenital myasthenic syndromes and myopathies. Focus should be on identifying potentially treatable NMDs such as Pompe disease or the congenital myasthenic syndromes. Even so, many individuals will remain without a confirmed genetic diagnosis as certain disorders are not amenable to detection via NGS and acquired disorders may mimic an inherited myopathy. Assays such as exome, genome, and RNA sequencing will likely play an increasing role in the genetic evaluation of undiagnosed muscle and neuromuscular junction disorders.

Volodarsky et al. (2021) performed comprehensive sequencing and CNV analysis of 34 Charcot-Marie-Tooth (CMT) disease-associated genes in a cohort of 2517 individuals with suspected CMT disease. The researchers identified many novel pathogenic variants, as well as VUSs. Overall diagnostic yield was 15% in males and 21% in females. The authors noted that this study expanded the mutational continuum of CMT disease-related genes and supported the clinical utility of comprehensive sequencing and copy number analysis for individuals suspected of having CMT disease.

Vogt et al. (2020) evaluated the clinical utility of genetic screening in patients presenting to a neuromuscular clinic with neuropathy without a confirmed etiology. The testing consisted of a NGS-based inherited neuropathy panel of 72-81 genes. Of the 200 participants screened, 30 had pathogenic mutations. 83.3% of the positive mutations were found in the *PMP22*, *TTR,* and *GJB1* genes. In four participants, the identification of a pathogenic mutation altered their management. Two participants undergoing treatment for demyelinating autoimmune neuropathy were diagnosed with CMT disease subtypes. The researchers determined that in this small study, although only a minority of participants with suspected inherited neuropathy tested positive, screening did alter their clinical management.

Winder et al. (2020) evaluated the diagnostic yield of genetic testing for hereditary NMDs through NGS-based gene panel analysis of 25,356 unrelated individuals with a suspected NMD, using subsets of 266 genes. The panels were designed using published gene/disorder and genotype-phenotype associations, as well as modes of inheritance and differential diagnoses. A definitive diagnosis was determined in 5055 (20%) of the participants. CNVs accounted for up to 39% of the significant variants found. Multi-gene testing addressed differential diagnoses in at least 6% of individuals with positive results. This large study provided additional direction for clinicians who use genetic tests to diagnose NMDs.

Haskell et al. (2018) conducted a prospective cohort study to evaluate the diagnostic utility of WES in 93 participants with suspected NMDs who had previously undergone unrevealing diagnostic workups. The study population included individuals aged 0 to 77 years (mean age 44) enrolled through the North Carolina Clinical Genomic Evaluation by Next-generation Exome Sequencing (NCGENES) study. WES was performed using Agilent SureSelect XT kits and Illumina HiSeq2500 sequencing, with variant analysis guided by three diagnostic gene lists: neuropathy (199 genes), myopathy (181 genes), and a broad NMD list (482 genes) comprising the neuropathy and myopathy lists and over 100 additional genes. The overall diagnostic yield was 12.9%, with pathogenic or likely pathogenic variants identified in 12 participants. Focused gene lists yielded similar diagnostic rates to the broad list in participants with clear neuropathy (14.3%) or myopathy (16.1%) phenotypes. In participants with complex phenotypes, the broad list provided a higher yield (9.8%) compared to the neuropathy (4.9%) or myopathy (0%) lists. WES led to changes in clinical management in at least two cases. The authors concluded that genome-scale sequencing or targeted gene panels used early in the diagnostic process can clarify diagnoses and reduce the need for invasive testing in patients with NMDs, particularly in complex cases. Study strengths included a well-characterized cohort, systematic comparison of gene list strategies, and integration of prior diagnostic data. Limitations included potential selection bias due to enrollment of participants with extensive prior

testing, exclusion of known diagnoses, inability of WES to capture intronic variants that may have an association with disease, and the use of singleton rather than trio sequencing, which may have reduced diagnostic yield.

Clinical Practice Guidelines

American Academy of Neurology (AAN) and American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM)

Kang et al. (2015, reaffirmed 2024). authored the joint AAN and AANEM evidence-based guidelines for genetic testing in the evaluation and diagnosis of congenital muscular dystrophy (CMD). In many situations, CMD can be diagnosed clinically based on a characteristic phenotype, histological results, and other clinical tests. However, genetic diagnosis is beneficial to the affected individual, as it often enables physicians to provide more accurate prognoses and facilitate genetic counseling and family-planning discussions. Genetic diagnoses also may enable individuals to participate in clinical trials. The AAN and AANEM guidelines include the following:

- Physicians caring for children with CMD should consult a pediatric neuromuscular specialist for diagnosis and management (Level B).
- When available and feasible, physicians might order targeted genetic testing for specific CMD subtypes that have well-characterized molecular causes (Level C).
- In individuals with CMD who either do not have a mutation identified in one of the commonly associated genes or have a phenotype whose genetic origins have not been well characterized, physicians might order whole exome or whole genome sequencing when those technologies become more accessible and affordable for routine clinical use (Level C).

American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), and American Academy of Physical Medicine and Rehabilitation (AAMPR)

England et al. (2009, reaffirmed 2025) reviewed the available literature to develop the following joint AAN, AANEM and AAMPR evidence-based guidelines for laboratory and genetic testing in the assessment of distal symmetric polyneuropathy, including an evidence-based, tiered approach to evaluation.

- Genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies (Level A).
- Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype (Level C).
- Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features and should focus on the most common abnormalities which are *CMT1A* duplication/HNPP deletion, Cx32 (*GJB1*), and *MFN2* mutation screening.
- There is insufficient evidence to determine the usefulness of routine genetic testing in patients with cryptogenic polyneuropathy who do not exhibit a hereditary neuropathy phenotype.

American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM)

Kassardjian et al. (2016, reaffirmed 2021) developed the AANEM position statement regarding the utility of genetic testing in neuromuscular disease (NMD). The goal of the statement was to generally endorse genetic testing as a component of diagnosing NMD, but not to endorse a specific test or testing algorithm. The authors provided a consensus opinion from an expert panel that highlighted the benefits of genetic testing including reduced time to diagnosis, avoidance of unnecessary testing, improved surveillance and monitoring, family testing and family planning, and better access to research and clinical trials. The authors noted that recommendations and guidelines exist that direct the selection of appropriate genetic tests. Specifically cited was the AANEM evidence-based guidelines for the diagnosis of CMD (Kang et al. 2015; reaffirmed 2024).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Laboratories that perform genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm. (Accessed May 16, 2025)

Refer to the following website for a list of nucleic acid-based tests/platforms that have been cleared or approved by the FDA's Center for Devices and Radiological Heath: https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. (Accessed May 16, 2025)

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Policy History/Revision Information

Date	Summary of Changes

11/01/2025	**Title Change**
	• Previously titled *Genetic Testing for Neuromuscular Disorders*
	Coverage Rationale
	• Revised language to indicate:
	  ○ Multi-gene Targeted Panel testing (five or more genes) for neurological disorders is proven and medically necessary when all of the following criteria are met:
	  ▪ The individual to be tested displays signs or symptoms of a heritable neurological disorder and the results are expected to directly impact medical management of that disorder
	  ▪ The test is ordered by or in consultation with a medical geneticist, developmental pediatrician, or adult or pediatric neuromuscular or neurogenetics specialist
	  ▪ The test is intended to establish a genetic cause for any one of the following:
	  – Congenital or Metabolic Myopathy
	  – Ataxia
	  – Peripheral neuropathy
	  – Hereditary spastic paraplegia
	  – Muscular dystrophy

Date	Summary of Changes
	○ Comprehensive Panel tests intended to evaluate multiple genes associated with multiple categories of clinically distinct neurological disorders are unproven and not medically necessary due to insufficient evidence of efficacy ○ Whole Exome and Whole Genome Sequencing are addressed in the Medical Policy titled *Whole Exome and Whole Genome Sequencing (Non-Oncology Conditions)* **Medical Records Documentation Used for Reviews** • Updated list of Medical Records Documentation Used for Reviews: ○ Added: ▪ Signs or symptoms of the individual being tested ▪ Name and specialty of the ordering and/or consulting provider ▪ Medical condition(s) for which the test is intended to establish a genetic cause ○ Removed: ▪ Personal history of the condition, if applicable, including age at diagnosis ▪ Complete family history (usually three-generation pedigree) relevant to condition being tested ▪ Genetic testing results of family member, if applicable, and reason for testing ▪ Ethnicity/ancestry (e.g., Ashkenazi Jewish), if reason for testing ▪ Any prior genetic testing results ▪ Genetic counseling (if available) ○ Replaced "*how* clinical management will be impacted based on results of genetic testing" with "*whether* clinical management will be *directly* impacted based on results of genetic testing" **Definitions** • Added definition of: ○ Ataxia ○ Comprehensive Panel ○ Congenital Myopathy ○ Metabolic Myopathy ○ Targeted Panel • Removed definition of: ○ Comparative Genomic Hybridization (CGH) ○ Neuromuscular Disorders (NMD) ○ Next Generation Sequencing (NGS) ○ Variant of Unknown Significance (VUS) **Applicable Codes** • Removed CPT codes 0417U, 81440, 81460, and 81465 **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version 2025T0598L

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the

independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.