Genetic Testing for Neurological Disorders

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➲ Instructions for Use

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Related Commercial/Individual Exchange Policies

- Whole Exome and Whole Genome Sequencing (Non-Oncology Conditions)

Community Plan Policy

- Genetic Testing for Neurological 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

Targeted Panel testing of 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 has 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 of the following:
  - Congenital Myopathy 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: For whole-exome and whole-genome sequencing, refer to the Medical Policy titled Whole Exome and Whole Genome Sequencing (Non-Oncology Conditions).

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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 nonoverlapping 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, multiminicore 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 nonspecific clinical presentation (Rehder et al., 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

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Description of Services

Genetic testing for neurological disorders is intended to assist individuals and health care providers with determining a diagnosis and/or prognosis, determining the risk of developing a disorder, and identifying appropriate clinical interventions.

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Neurological disorders include neurodegenerative conditions, neuromuscular conditions, and other conditions affecting the brain, spine, or peripheral nerves. 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, Charcot-Marie-Tooth disease, hereditary sensory and autonomic neuropathy, hereditary motor neuropathy, hereditary neuropathy with liability to pressure palsies, hereditary spastic paraplegia, 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 hereditary spastic paraplegia (Fereshtehnejad et al., 2023).

This policy addresses multigene 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 in individuals with signs or symptoms of heritable neurological disorders. Studies consistently show that an individual's phenotype typically correlates with variants in genes that are already known to be associated with that clinical presentation. This genotype-phenotype relationship supports the use of targeted panel testing for accurate diagnosis and informed clinical decision-making. In contrast, comprehensive panels assess genes that are unrelated to the individual's phenotype and lack supporting clinical evidence at this time.

The Ayala-Ramírez et al. (2026) observational, single-center cohort study aimed to characterize the genetic causes of hereditary myopathies in a cohort of 175 male individuals who were referred for genetic evaluation between 2016 and 2018. Individuals were included if there was clinical suspicion of hereditary myopathy and creatine kinase (CK) was elevated. The cohort included 141 children (80.6%; mean age, 8.6 years; range, 9 months to 17 years) and 34 adults (19.4%; mean age, 29.4 years; range, 18 to 61 years). All individuals underwent first-line testing for *DMD* gene copy number variants (CNVs), followed by targeted next-generation sequencing (NGS) using a 56-gene panel for any individuals with negative or indeterminate CNV results. This sequential testing approach produced an overall diagnostic yield of 85.7% (150 of 175 cases). Pathogenic *DMD* variants were identified in 44.6% (n = 78), including 56 with deletions (71.8%) and 22 with duplications (28.2%). Among the 97 individuals who were undergoing NGS, pathogenic or likely pathogenic variants were identified in 74.2% (n = 72), with clustered in 17 of the 56 genes included in the NGS panel (30.4%). Duchenne/Becker muscular dystrophy was the most frequent diagnosis, accounting for 74.3% (n = 130) overall and 53.6% (n = 52) among those who were undergoing NGS, while limb-girdle muscular dystrophies were identified in 5.7% (n = 10). Variants of uncertain significance (VUSs) were identified in 43.3% of individuals (n = 42) who were undergoing NGS. Subgroup analyses showed a diagnostic yield of 88.7% in children (n = 125), with a Duchenne/Becker muscular dystrophy diagnosis identified in 82.3% (n = 116), compared with a subgroup diagnostic yield of 73.5% in adults (n = 25). The authors concluded that a sequential diagnostic strategy that combines CNV detection and targeted NGS improves the molecular diagnosis of hereditary myopathies and supports clinical management and genetic counseling. Limitations of this study include the observational design without a comparator group and referral-based sampling that may limit generalizability.

Hayes (2025) published a Precision Medicine Research Brief that described the published literature related to the use of Genomic Unity Movement Disorders Analysis (Variantyx Inc.) for the diagnosis of movement disorders. Hayes did not identify any abstracts that addressed the test's clinical utility or evaluated the test's performance. Hayes concluded that there is no/unclear support for the test in clinical practice guidelines and position statements because no relevant position statements or guidelines were identified that addressed the use of Genomic Unity Movement Disorders Analysis for the diagnosis of movement disorders. The paucity of published, peer-reviewed literature precluded further evidence evaluation.

The Muelas et al. (2025) observational cohort study analyzed individuals with distal myopathies who were followed up at a single neuromuscular reference center, combining retrospective identification and prospective follow-up from January 2016 through December 2022, with the objective of characterizing clinical features and factors associated with achieving a molecular diagnosis. Participation required confirmed distal muscle involvement of a presumed myopathic origin and a suspected genetic etiology. The cohort comprised 219 individuals from 156 families; 61% were male, with a mean age at onset of 29 years and a mean follow-up period of 12.4 years. The inheritance pattern was sporadic in 41%; 40.5% and 15% had dominant and recessive inheritance, respectively. Genetic testing evolved over time and included Sanger sequencing and NGS approaches, such as comprehensive neuromuscular gene panels, targeted myopathy panels, and targeted exome sequencing; 96.4% of the study individuals underwent genetic testing. Molecular diagnosis was achieved in 68.7% (144 of 209 cases), identifying variants across 19 genes, with 85% of the variants concentrated in *MYH7*, *ANO5*, *DYSF*, *TTN*, *MYOT*, *HSPB1*, *GNE*, and *HNRNPDL*. The mean time to genetic diagnosis was 7 years overall (11.57 years in individuals who had been tested before 2016 vs 1.85 years in those who were tested after NGS implementation in

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2016). Logistic regression showed a lower likelihood of diagnosis in individuals who presented with late-onset disease [odds ratio (OR), 0.286; 95% CI, 0.1-0.7; p < 0.01] and a higher likelihood of diagnosis in familial cases (OR, 6; 95% CI, 2.35-16.5; p < 0.01); normal serum CK (OR, 14.2; 95% CI, 2.4-152.4; p < 0.05); or neuromyopathic histological features (OR, 7.4; 95% CI, 1.4-48.7; p < 0.05). The electromyography pattern was not predictive, with myopathic electromyography patterns in 67.2% of cases, neurogenic patterns in 17%, mixed patterns in 12%, and spontaneous activity in 58%. Other ancillary findings included elevated serum CK in 69.6%, while characteristic magnetic resonance imaging patterns were noted in 73.5% of molecularly diagnosed index cases. The authors concluded that distal myopathies are genetically heterogeneous, with distinct features that may aid in their diagnosis, and that NGS improves diagnostic yield while shortening the time to results. Limitations of this study include the single-center, noncomparative, observational design; evolving genetic testing methodologies over time; and the high proportion of individuals (> 30%) who remained without a molecular diagnosis. Additional constraints include this study's potential selection and referral bias, heterogeneity in testing methods, and absence of standardized prospective outcome measures across all individuals.

The Kulsirichawaroj et al. (2025) combined prospective and retrospective single-center cohort study evaluated the diagnostic yield and clinical impact of NGS, including targeted gene panel testing and exome sequencing, in 135 individuals with pediatric-onset suspected genetic neuromuscular disorders (NMDs) who remained undiagnosed after conventional testing at a single referral center between 2020 and 2024. Individuals who were younger than 21 years were recruited through a tertiary pediatric neuromuscular clinic and underwent phenotype-directed genetic testing; 44 underwent panel testing, and 112 underwent exome sequencing. The median age at onset was 2.0 years (IQR, 0.5-4.0 years), 60.7% were male, and 23.0% reported a family history of neuromuscular disease. The median time from symptom onset to the first NGS test was 4.8 years (IQR, 2.2-9.2 years) and to genetic diagnosis was 5.7 years (IQR, 2.5-10.7 years). Results were classified as positive, probable, possible, or negative, and diagnostic yield was defined as the proportion of positive or probable cases. The overall diagnostic yield was 69.6% (94 of 135 cases), including 68 positive and 26 probable cases, with subgroup yields of 70.7% (53 of 75 cases) for inherited myopathies, 63.3% (31 of 49 cases) for inherited neuropathies, 90.0% (nine of 10 cases) for congenital myasthenic syndromes, and 100% (one case) for motor neuron disease. Among inherited myopathies, the diagnostic yield was 63.2% (36 of 57 individuals) after excluding Duchenne muscular dystrophy (DMD), and among Charcot-Marie-Tooth disease cases, 65.9% (29 of 44 individuals) had pathogenic or likely pathogenic variants. Genetic diagnoses influenced clinical management in 87.2% of the diagnosed cases, including diagnostic revisions in 12 individuals, avoidance of unnecessary investigations in 26, initiation of targeted therapies in 34 (36.2%), surveillance changes in 76 (80.9%), family counseling in 57 (60.6%), and prognostic clarification in 82 (87.2%). The authors concluded that gene panel testing and exome sequencing substantially improve diagnostic accuracy and clinical management in pediatric NMDs and support integration of NGS into diagnostic workflows. Limitations of this study include its single-center design, with potential selection bias toward complex cases; absence of a control group; lack of randomization and masking; possible subjectivity in variant classification; and small subgroup sample sizes. An additional limitation is the lack of reported statistical comparisons.

The Karthikeyan et al. (2024) retrospective, observational diagnostic cohort study evaluated 961 unrelated male patients who were aged 2 to 35 years with clinically suspected DMD using a sequential molecular testing algorithm that emphasized NGS as the central diagnostic modality after initial screening. Patients first underwent targeted *DMD* gene screening; the 246 patients without detected *DMD* variants were subsequently evaluated using a targeted NGS muscular dystrophy panel. NGS identified small *DMD* variants that had been undetectable by the screening assay in an additional 101 patients. Among the 145 patients without *DMD* variants, NGS reclassified 100 as having other muscular dystrophies, demonstrating the capacity of NGS to detect genetically heterogeneous conditions with overlapping clinical phenotypes. In this subgroup, NGS enabled identification of recurrent variants and potential founder effects, including an *SGCB* c.544A > C variant that was present in 18 unrelated patients (62%) with limb-girdle muscular dystrophy (LGMD) type 2E. The authors concluded that incorporation of NGS into the diagnostic workflow substantially improves diagnostic accuracy in individuals with DMD-like presentations by identifying alternative genetic etiologies that are not detectable through traditional gene-targeted methods. The findings highlight that reliance on clinical presentation alone would have led to misclassification in approximately 15% of cases in this study and that NGS enables differentiation among phenotypically overlapping muscular dystrophies, especially autosomal recessive LGMDs. However, interpretation of NGS results was limited by the high proportion of VUSs returned and the presence of multiple co-occurring variants in some patients, which precluded definitive attribution of causality in all cases. Additional limitations of the study include the absence of a comparison group and lack of masking, which constrain generalizability.

The Barreto Tenorio et al. (2024) systematic review evaluated the diagnostic yield of NGS for hereditary ataxia by synthesizing 33 eligible studies that were published between 2016 and 2022, comprising 3,144 individuals who were tested in tertiary centers. The primary studies used cohort, case-control, cross-sectional, and case series designs. Individuals with ataxia as a major feature underwent targeted NGS panel testing, whole-exome sequencing (WES), or whole-genome sequencing (WGS), with diagnostic yield defined as the proportion with pathogenic or likely pathogenic germline variants. The median diagnostic yield across studies was 43% (IQR, 9.5%-100%), with median yields of 46% for

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NGS and 41.9% for WES. WGS was infrequently used and reported yields of 20% (four of 20) and 33% (12 of 35) in two studies. Diagnostic yields varied substantially by cohort selection and clinical characteristics, ranging from 9.5% (39 of 142) to 100% (19 of 19), and was higher in phenotype-specific cohorts (median, 68.35%) compared with selected (40.45%) and unselected cohorts (30.5%). The yield was greater in presumed autosomal recessive inheritance (median, 62.5%) and in cohorts with parental consanguinity (median, 52.4% vs 32%; p = 0.009) and differed by prior testing strategies, with studies omitting tandem repeat expansion screening that demonstrated a higher yield (median, 74.2% vs 37.7%; p = 0.047). Early-onset (defined as presenting before age 25-30 years) and late-onset cohorts had median yields of 46.6% and 54.5%, respectively. The most frequently identified genes included *SACS* and *CACNA1A*, with additional recurrent findings in *SYNE1*, *SETX*, and *SPG7*, and a median yield of VUSs of 20.6% (IQR, 8%-33.6%) reported across 15 studies. The authors concluded that NGS provides substantial diagnostic yield in hereditary ataxia, particularly in cohorts enriched for autosomal recessive inheritance patterns, positive family history, or consanguinity. Interpretation is limited by marked heterogeneity across the included studies in cohort selection, prior workup, phenotype definitions, and testing strategies; the predominance of observational, nonrandomized designs without consistent comparators; and incomplete reporting of statistical measures such as CIs for many outcomes. Additional limitations include selection bias in phenotype-enriched or prescreened cohorts; limited generalizability due to geographic and ancestry concentration; inconsistent reporting of prior genetic testing and attrition; and the inability of NGS to detect repeat expansions, which is a common etiology of hereditary ataxia.

Alhammad et al. (2024) conducted a retrospective cohort study to characterize the clinical and genetic spectrum of hereditary myopathies in an adult Saudi Arabian population. The study reviewed the medical records of 87 patients from 78 families who were evaluated at a tertiary hospital in Riyadh between January 2018 and December 2022. The testing methodologies used included WES, WGS, an NGS neuromuscular panel, and single-gene or targeted analysis, chosen at the discretion of the treating physician. However, 24 patients did not undergo genetic testing due to unavailability or unspecified reasons. The most common clinical diagnosis among those tested was 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 was found to have pathogenic or likely pathogenic genetic variants. Among these 26 patients, the genetic testing methods used had been 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, limited-resource setting, in which there was restricted availability of immunohistochemical stains and mitochondrial genome sequencing technologies, which potentially overestimated the diagnostic yield of the genetic analysis reported here.

Ebert et al. (2024) retrospectively examined the clinical usefulness and detection rate of genetic testing in patients with suspected NMDs at a single, large neuromuscular center. The authors analyzed the medical records of 192 patients who underwent multigene panel testing for NMDs (defined as neuropathy, myopathy/nondystrophic myotonia, neuromuscular junction disease, or motor neuron disease), using either a 230-gene NMD panel or a 111-gene neuropathy panel from a single laboratory. Pathogenic variants, VUSs, or both were identified in 77.1% of cases, with a definitive diagnosis established in 35.9%. Suspected neuropathy was the most common testing indication (53.3%), whereas myopathy had the highest diagnostic yield (48.7%). The main limitations of this study are its single-center design, which indicates that the findings may not be generalizable, and the exclusion of specimens sent to other laboratories during the study period. Furthermore, this study is limited by its exclusive focus on multigene panel testing. 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.

Radziwonik-Fraczyk et al. (2024) conducted a prospective cohort study to evaluate the diagnostic utility of a custom-designed NGS panel in participants with NMDs who presented with heterogeneous clinical phenotypes. The study included 52 Polish participants who underwent genetic testing using a targeted NGS panel of 89 genes. Additional testing included genotyping for myotonic dystrophy types 1 and 2 and multiplex ligation–dependent probe amplification (MLPA) for CNV detection. A molecular diagnosis was achieved in 29 participants (55.8%) using the NGS panel alone. When combined with genotyping and MLPA, the diagnostic yield increased to 57.7% (30 of 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 participants, which suggests possible complex inheritance patterns. MLPA analysis confirmed a *CAPN3* exon 2-8 deletion in one participant, which was consistent with LGMD type R1. The study identified 27 known and four 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 participants further supports the need for comprehensive genetic

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evaluation in this population of individuals. Limitations of this study include incomplete clinical data (e.g., CK levels, muscle biopsy) for some participants 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 6,849 adult patients who underwent clinician-ordered testing using panels that ranged from 66 to 111 genes, incorporating both NGS and intragenic deletion/duplication analysis. A molecular diagnosis was identified in 8.4% of patients (573 of 6,849). 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 of 573) had clinically actionable findings. 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 individuals 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, which is 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 patients (ages 6 months to 67 years) who were suspected to have a genetic NMD based on clinical examination, laboratory findings, and imaging. Patients who had been diagnosed previously with a dystrophinopathy following MLPA genetic analysis were excluded. The genes that were 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 patients were found to have a genetic basis for their disorder, correlating to a diagnostic yield of 46%. Overall, 23 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 patients, including patients with a VUS, patients who were heterozygous for an autosomal recessive disease, and patients who were found to have variants 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 use of WES.

Ceylan et al. (2023) retrospectively evaluated the role of targeted NGS panels in the molecular diagnosis of Charcot-Marie-Tooth disease in routine clinical practice, highlighting both their utility and limitations. Molecular techniques included MLPA, NGS, and WES. MLPA identified pathogenic variants in 25 of 64 patients with suspected Charcot-Marie-Tooth (39%), including 14 with *PMP22* duplications and 11 with *PMP22* deletions. Among 50 patients who underwent targeted NGS panel testing, 36% had pathogenic or likely pathogenic variants. Five patients with negative NGS results subsequently underwent WES, which yielded a diagnostic rate of 80%. The authors determined that in this study, a targeted NGS panel was diagnostic in approximately one-third of patients after ruling out *PMP22* deletion/duplication. They advocated for an algorithmic molecular approach to genetic evaluation, along with genetic counseling, pedigree analysis, and further study to uncover additional information related to the etiology of Charcot-Marie-Tooth 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 1,413 genetically confirmed HSP cases from 202 eligible studies that were published between 1990 and June 2018; 767 individuals had movement disorders (HSP-MD), and 646 did not (HSP-nMD). The study population included individuals with a wide range of spastic paraplegia genotypes, with spastic paraplegia 11 (SP11; 27.7%) and spastic paraplegia 7 (SP7; 18.1%) being the most common. The HSP-MD group had a significantly older age at onset (20.5 ±16.0 years) compared with 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%). SP7 was most frequently associated with ataxia, while SP11 was most commonly linked to parkinsonism, dystonia, and cognitive impairment. Key findings included significant phenotypic differences between SP7 and SP11 in the HSP-MD group. SP7 was associated with later onset, ataxia, extraocular movement disturbances, and seizures. In contrast, SP11 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 in which genetic testing may be unavailable or inconclusive. The strengths of the study include the use of IPD meta-analysis, which allowed for detailed statistical comparisons and for the inclusion of rare genotypes that are typically excluded from conventional meta-analyses. Limitations include the potential underrepresentation of HSP-nMD cases due to the search strategy, the

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exclusion of studies that were published after 2018, and challenges with missing or nonstandardized data due to inconsistent clinical assessment and reporting across studies. Furthermore, the prevalence of rare phenotypes and genotypes may be overestimated due to this study's reliance on published case reports that may introduce bias toward 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 in 155 adults and children who were seen in an NMD clinic during a 3-year period. The primary objective was to improve genetic testing decisions and counseling for patients with NMDs because an inaccurate or delayed diagnosis can negatively impact a patient's medical treatment. The authors focused on patients with elevated CK levels and muscle weakness, which were the most common findings associated with referrals to the NMD clinic. In total, 26 unique genetic tests were used, with diagnostic yields ranging from 0% to 66%. Over half of the patients underwent testing with a comprehensive neuromuscular panel that included between 110 and 211 genes that are known to be associated with muscular dystrophies, inherited myopathies, and congenital myasthenic syndromes. Overall, 262 individual tests were ordered (an average of 1.7 tests per patient); 21% of the patients who were tested received a genetic diagnosis. The clinical finding that was most associated with a diagnostic result was elevated CK, with or without muscle weakness. All patients who were diagnosed with Duchenne, Emery-Dreifuss, limb-girdle, or Becker muscular dystrophy had an elevated CK level, as did patients with any of several congenital myopathies. Additionally, all patients who were diagnosed with a myopathy presented with muscle weakness, as did half of the patients who were diagnosed with a muscular dystrophy. The authors concluded that the presence of elevated CK, muscle weakness, or both should prompt careful clinical assessment for these disorders and consideration of genetic testing. Study limitations include the small sample size, limited data availability due to the study design (retrospective chart review), and limited generalizability of the findings to diverse populations.

Schuermans et al. (2023) evaluated the diagnostic yield of exome sequencing–based multigene panel testing in patients with adult-onset neurological disorders in a retrospective observational study. A cohort of 1,411 patients were selected for targeted exome sequencing–based multigene panels that included 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 that are associated with amyotrophic lateral sclerosis was introduced to the study in 2021. A genetic diagnosis was identified in 10% of the total cases, comprising 71 different monogenic disorders. The highest diagnostic yield was seen in patients who presented with ataxia or spastic paraparesis (19%), but the yield 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 neurological diseases.

Barbosa-Gouveia et al. (2022) conducted a prospective multicenter study of the diagnostic utility of multigene panel testing in the evaluation of 268 participants (aged 0-80 years) with a suspected inherited NMD. Three versions of the multigene panel were applied during the 3-year study period, with a progressive addition of genes to each version. The diagnostic yield of the first panel (278 genes) was 31%; the diagnostic yield of the third panel (324 genes) increased to 40%. The mean diagnostic yield for the entire 3-year study period was 36%, which is a value within range of reported diagnostic yields for targeted sequencing panels, clinical exome sequencing, and WES, according to the authors. In this study, the most common diagnoses that were identified were muscular dystrophies/myopathies (68.4%) and peripheral nerve diseases (22.5%). Variants in *TTN*, *RYR1*, and *ANO5* contributed to nearly 30% of the overall diagnosed cases. Based on the results of this study, the authors recommended comprehensive panel testing in individuals with suspected inherited NMDs. However, the study is limited by its small number of participants. Further evaluations, including high-quality studies with larger cohorts, are needed to support their suggestion.

Clinical Practice Guidelines

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

Kang et al. (2015; reaffirmed 2025) 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 patient, as it often enables physicians to provide more accurate prognoses and facilitate genetic counseling and family-planning discussions. Genetic diagnoses also may enable patients 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).

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- When available and feasible, physicians might order targeted genetic testing for specific CMD subtypes that have well-characterized molecular causes (level C).
- In patients with CMD who either do not have a mutation identified in one of the commonly associated genes or have a phenotype with genetic origins that have not been well characterized, physicians might order WES or WGS when those technologies become more accessible and affordable for routine clinical use (level C).

The American Academy of Pediatrics, the American Occupational Therapy Association, the Child Neurology Society, and the National Association of Neonatal Nurses endorsed the joint AAN/AANEM guidelines.

Narayanaswami et al. (2015; reaffirmed 2023) authored the joint AAN/AANEM guidelines for the diagnosis and treatment of limb-girdle and distal dystrophies. The guidelines recommend that clinicians use a clinical approach to guide genetic diagnosis of patients with suspected muscular dystrophy, based on clinical phenotype, inheritance pattern, and associated manifestations (level B recommendation). The guidelines also list recommended phenotype-driven targeted testing strategies (often single-gene analysis) for known genotype/phenotype correlations. Additionally, the guidelines include the following recommendations for the use of targeted panel testing:

- In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal dominant inheritance, cardiomyopathy, respiratory involvement, electromyography with myotonic or pseudomyotonic discharges, ankle dorsiflexor weakness, and muscle biopsy (if performed) with features of myofibrillar myopathy, clinicians should perform genetic testing for mutations in the following genes (level B recommendation).
  - *CRYAB* (αB-crystallin dystrophy)
  - *DES* (muscular dystrophy, limb-girdle, type 1E)
  - *DNAJB6* (autosomal dominant LGMD type 1D)
  - *FLNC* (filamin C-associated dystrophy)
  - *MYOT* (LGMD type 1A)
  - *TTN* (titin-related muscular dystrophy)
  - *ZASP* (ZASP-related myofibrillar myopathy)
- In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance and mental retardation, clinicians should screen for mutations in the following genes that cause primary or secondary deficiency of α-dystroglycan (level B recommendation).
  - *DAG1* (autosomal recessive LGMD type 2P)
  - *FKTN* (muscular dystrophy-dystroglycanopathy type C4)
  - *POMGNT1* (autosomal recessive LGMD type 2O)
  - *POMT1* (autosomal recessive LGMD type 2K)
  - *POMT2* (autosomal recessive LGMD type 2N)
- In patients with muscular dystrophy who have proximal as well as distal weakness, clinicians should use specific clinical features (e.g., rippling muscles, cardiomyopathy, atrophy of specific muscle groups, irritability on electromyography) and biopsy features (myofibrillar myopathy, reduction of emerin immunostaining, presence of rimmed vacuoles) to guide genetic testing, which may include mutations in the following genes (level B recommendation).
  - *ANO5* (autosomal recessive LGMD type 2L)
  - *BAG3* (BAG3-associated dystrophy)
  - *CAV3* (LGMD type 1C)
  - *CRYAB* (αB-crystallin dystrophy)
  - *DES* (muscular dystrophy, limb-girdle, type 1E)
  - *DNAJB6* (autosomal dominant LGMD type 1D)
  - *DYSF* (LGMD type 2B)
  - *EMD* (Emery-Dreifuss muscular dystrophy)
  - *FLNC* (filamin C–associated dystrophy)
  - *LMNA* (Emery-Dreifuss muscular dystrophy)
  - *MYOT* (LGMD type 1A)
  - *TTN* (titin-related muscular dystrophy)
  - *ZASP* (ZASP-related myofibril myopathy)
- In patients with suspected muscular dystrophy in whom initial genetic testing, muscle biopsy, and dried blood spot test for Pompe disease do not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, WES, whole-genome screening, or NGS to identify the genetic abnormality (level C recommendation).

The American Academy of Physical Medicine and Rehabilitation and the Child Neurology Society endorsed the joint AAN/AANEM guidelines.

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American Academy of Neurology (AAN)/American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM)/American Academy of Physical Medicine and Rehabilitation (AAPMR)

England et al. (2009; reaffirmed 2025) reviewed the available literature to develop the following joint AAN, AANEM, and AAPMR 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 have 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/deletion and mutations in *GJB1* or *MFN2* (level of recommendation not listed).
- There is insufficient evidence to support or refute the usefulness of routine genetic testing in patients with cryptogenic polyneuropathy without a hereditary neuropathy phenotype (level U).

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 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, such as the AANEM evidence-based guidelines for the diagnosis of CMD (Kang et al., 2015).

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 act of 1988. More information is available at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm. (Accessed May 1, 2026)

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 1, 2026)

References

Alhammad RM, Alrehaili ML, Albulaihe HM, et al. Clinical and genetic evaluation of hereditary myopathies in an adult Saudi cohort. BMC Neurol. 2024 Sep;24(1):312.

Ayala-Ramírez P, García-Acero M, Guerra-Torres M, et al. Genetic causes of hereditary myopathies in a cohort of male patients: molecular diagnosis in myopathies. J Appl Lab Med. 2026 Jan;11(1):15-25.

Barbosa-Gouveia S, Vázquez-Mosquera ME, González-Vioque E, et al. Rapid molecular diagnosis of genetically inherited neuromuscular disorders using next-generation sequencing technologies. J Clin Med. 2022 May;11(10):2750.

Barreto Tenorio R, Camargo CHF, Carvalho Donis K, et al. Diagnostic yield of NGS tests for hereditary ataxia: a systematic review. Cerebellum. 2024 Aug;23(4):1552-1565.

Çavdarlı B, Köken ÖY, Satılmış SBA, et al. High diagnostic yield of targeted next-generation sequencing panel as a first-tier molecular test for the patients with myopathy or muscular dystrophy. Ann Hum Genet. 2023 May;87(3):104-114.

Ceylan GG, Habiloğlu E, Çavdarlı B, et al. High diagnostic yield with algorithmic molecular approach on hereditary neuropathies. Rev Assoc Med Bras (1992). 2023 Feb;69(2):233-239.

Ebert SE, Meiling JB, Caress JB, et al. Clinical utility and diagnostic yield of genetic testing for inherited neuromuscular disorders in a single, large neuromuscular center. Neurol Clin Pract. 2024 Apr;14(2):e200268.

England JD, Gronseth GS, Franklin G, et al. Practice parameter: the evaluation of distal symmetric polyneuropathy: the role of laboratory and genetic testing (an evidence-based review): report of the American Academy of Neurology, the

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American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. PM R. 2009 Jan;1(1):5-13.

Fereshtehnejad SM, Saleh PA, Oliveira LM, et al. Movement disorders in hereditary spastic paraplegia (HSP): a systematic review and individual participant data meta-analysis. Neurol Sci. 2023 Mar;44(3):947-959.

Hayes, Inc. Precision Medicine Research Brief. Genomic Unity Movement Disorders Analysis (Variantyx Inc.). Hayes, Inc.; May 21, 2025.

Kang PB, Morrison L, Iannaccone ST, et al. Evidence-based guideline summary: evaluation, diagnosis, and management of congenital muscular dystrophy: report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular and Electrodiagnostic Medicine. Neurology. 2015 Mar;84(13):1369-1378.

Karthikeyan P, Kumar SH, Khanna-Gupta A, et al. In a cohort of 961 clinically suspected Duchenne muscular dystrophy patients, 105 were diagnosed to have other muscular dystrophies (OMDs), with LGMD2E (variant *SGCB* c.544A > C) being the most common. Mol Genet Genomic Med. 2024 Nov;12(11):e2123.

Kassardjian CD, Amato AA, Boon AJ, et al. The utility of genetic testing in neuromuscular disease: a consensus statement from the AANEM on the clinical utility of genetic testing in diagnosis of neuromuscular disease. Muscle Nerve. 2016 Dec;54(6):1007-1009.

Kulsirichawaroj P, Chanvanichtrakool M, Wattanadilokchatkun P, et al. Next-generation sequencing for pediatric-onset neuromuscular disorders unresolved by conventional diagnostic methods. Pediatr Res. 2025 Dec;98(6):2195-2202.

Manta A, Spendiff S, Lochmüller H, et al. Targeted therapies for metabolic myopathies related to glycogen storage and lipid metabolism: a systematic review and steps towards a 'treatabolome'. J Neuromuscul Dis. 2021;8(3):401-417.

Muelas N, Carretero-Vilarroig L, Martí P, et al. Clinical features, mutation spectrum and factors related to reaching molecular diagnosis in a cohort of patients with distal myopathies. J Neurol. 2025 Jan;272(1):97.

Narayanaswami P, Carter G, David W, et al. Evidence-based guideline summary: diagnosis and treatment of limb-girdle and distal dystrophies: report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular and Electrodiagnostic Medicine. Neurology. 2015 Apr;84(16):1720-1721.

Radziwonik-Fraczyk W, Elert-Dobkowska E, Karpinski M, et al. Next generation sequencing panel as an effective approach to genetic testing in patients with a highly variable phenotype of neuromuscular disorders. Neurogenetics. 2024 Jul;25(3):233-247.

Rehder C, Bean LJH, Bick D, et al. ACMG Laboratory Quality Assurance Committee: next-generation sequencing for constitutional variants in the clinical laboratory, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021 Aug;23(8):1399-1415.

Roggenbuck J, Morales A, Ellis CA, et al. Diagnostic and clinical utility of comprehensive multigene panel testing for patients with neuropathy. J Peripher Nerv Syst. 2024 Sep;29(3):363-367.

Rosenberg A, Tian C, He H, et al. An evaluation of clinical presentation and genetic testing approaches for patients with neuromuscular disorders. Am J Med Genet A. 2023 Nov;191(11):2679-2692.

Schuermans N, Verdin H, Ghijsels J, et al. Exome sequencing and multigene panel testing in 1,411 patients with adult-onset neurologic disorders. Neurol Genet. 2023 Apr;9(3):e200071.

Zhang H, Chang M, Chen D, et al. Congenital myopathies: pathophysiological mechanisms and promising therapies. J Transl Med. 2024 Sep;22(1):815.

Policy History/Revision Information

Date	Summary of Changes

09/01/2026	**Related Policies**
	• Removed reference link to the Medical Policy titled:
	  ○ *Chromosome Microarray Testing (Non-Oncology Conditions)*
	  ○ *Genetic Testing for Cardiac Disease*
	Coverage Rationale
	• Replaced reference to "*multi-gene* Targeted Panel testing (five or more genes)" with "Targeted Panel testing of five or more genes"
	Definitions

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Date	Summary of Changes

	• Removed definition of:
	  ○ Whole Exome Sequencing (WES)
	  ○ Whole Genome Sequencing (WGS)
	Supporting Information
	• Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information
	• Archived previous policy version 2026T0598N

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, 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.

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