Genetic Testing for Neuromuscular Disorders (for Ohio Only)

Policy Number: CS165OH.A
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Instructions for Use

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Related Policies

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

Application

This Medical Policy only applies to the state of Ohio. Any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using Ohio Administrative Code 5160-1-01.

Coverage Rationale

Genetic testing of Neuromuscular Disorders may be covered in certain circumstances; refer to the InterQual® CP: Molecular Diagnostics:

- Charcot-Marie-Tooth (CMT) Hereditary Neuropathy
- Duchenne Becker Muscular Dystrophy (DBMD)
- Glycogen Storage Disease Type I (GSDI)
- Niemann-Pick Disease Type A and B
- Niemann-Pick Disease Type C
- Pompe Disease (Glycogen Storage Disease Type II)
- Spinal Muscular Atrophy (SMA)
- Whole Genome Sequencing (WGS), Whole Exome Sequencing (WES), and Chromosomal Microarray (CMA) for Congenital or Hereditary Disorders

Click here to view the InterQual® criteria.

Glycogen Storage Disease Type 1 (GSDI) and Pompe Disease (Glycogen Storage Disease Type II)

Multi-gene panel testing for the diagnosis of Neuromuscular Disorders is proven and medically necessary for suspected glycogen storage disease in:

- An adolescent or adult with:
  - Exercise intolerance, muscle weakness, and muscle cramps; **and**
  - Normal or equivocal CK results; **and**
  - One of the following conditions is met:

- Exercise testing is unavailable or uninformative; **or**
- Muscle biopsy is unavailable or uninformative; **or**
- Targeted genetic testing was negative

or

- An infant or child with:
  - Unexplained liver disease, or muscle weakness, or heart dysfunction; **and**
  - One of the following is met:
    - Muscle biopsy is unavailable or uninformative; **or**
    - Enzyme testing was unavailable or uniformative; **or**
    - Targeted genetic testing was negative

Definitions

Comparative Genomic Hybridization (CGH): CGH is a technology that can be used for the detection of genomic copy number variations (CNVs). Tests can use a variety of probes or single nucleotide polymorphisms (SNPS) to provide copy number and gene differentiating information. All platforms share in common that tumor (patient) and reference DNA are labelled with dyes or fluorescing probes and hybridized on the array, and a scanner measures differences in intensity between the probes, and the data is expressed as having greater or less intensity than the reference DNA (Piluso et al. 2011).

Neuromuscular Disorders (NMD): A group of inherited diseases that represent a number of conditions that result from impairment of nerves that control the muscles, or direct impairment of the muscles (Piluso et al. 2011).

Next Generation Sequencing (NGS): High-throughput DNA sequencing of large numbers of genes in a single reaction (Efthymiou et al. 2016).

Variant of Unknown Significance (VUS): A variation in a genetic sequence that has an unknown association with disease. It may also be called an unclassified variant (Efthymiou et al. 2016).

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 federal, state, or contractual requirements 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

CPT Code	Description
0417U	Rare diseases (constitutional/heritable disorders), whole mitochondrial genome sequence with heteroplasmy detection and deletion analysis, nuclear-encoded mitochondrial gene analysis of 335 nuclear genes, including sequence changes, deletions, insertions, and copy number variants analysis, blood or saliva, identification and categorization of mitochondrial disorder-associated genetic variants
81440	Nuclear encoded mitochondrial genes (e.g., neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including *BCS1L, C10ORF2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, AND TYMP*
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)
81460	Whole mitochondrial genome (e.g., Leigh Syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection
81465	Whole mitochondrial genome large deletion analysis panel (e.g., Kearns-Sayre syndrome, Chronic Progressive External Ophthalmoplegia), including heteroplasmy detection, if performed
81479	Unlisted molecular pathology procedure

Description of Services

Technologies used for genetic testing of Neuromuscular Disorders (NMD) can vary, and can include, but are not limited to, tests that evaluate variations in the genes, such as chromosome microarray and Next Generation Sequencing (NGS), as well as others that assess the gene products, such as gene expression arrays and microRNA analysis. The number of genes evaluated can range from a single gene to the whole exome or genome of an individual. Results of genetic testing may assist individuals and healthcare providers with determining a diagnosis, prognosis, and identification of appropriate clinical interventions (Savarese et al. 2016; Piluso et al. 2011; and Ghaoui et al. 2015). This policy addresses genetic test panels with five or more genes for NMD. Neuromuscular diseases that typically present with a cardiomyopathy and are caused by a variant in a cardiomyopathy gene are addressed in the Medical Policy titled Genetic Testing for Cardiac Disease (for Ohio Only) and those associated with Whole Exome Sequencing are addressed in the Medical Policy titled Whole Exome and Whole Genome Sequencing (Non-Oncology Conditions) (for Ohio Only).

Clinical Evidence

Neuromuscular Disorders (NMD)

NMD are a heterogenous group of conditions that are caused by impaired muscles and impaired nerves that control the muscles. Examples of NMD include muscular dystrophies, nerve conduction disorders such as Charcot-Marie-Tooth (CMT), motor neuron disease (MND), hereditary spastic paraplegia (HSP), spinal muscular atrophies (SMA), and neuromuscular junction disease (myasthenic syndromes). Common symptoms include muscle weakness, cramps, numbness, respiratory and cranial nerve palsies. Many of these disorders are inherited, and over 500 genes are implicated in causing NMD (Efthymiou et al., 2016).

In an observational study, Schuermans et al. (2023) evaluated the diagnostic yield of exome sequencing (ES) and multigene panel testing in individuals with adult-onset neurologic disorders, including neuromuscular disorders. A total of 1,411 individuals were tested using ES-based multigene panel testing. Panels for ataxia and spasticity, leukoencephalopathy, movement disorders, paroxysmal episodic disorders, neurodegeneration with brain iron accumulation, progressive myoclonic epilepsy, and amyotrophic lateral sclerosis were created and a total of 725 genes associated with Mendelian inheritance were included overall. 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%) and varied based on individual phenotype. The majority of diagnoses found included disorders with autosomal dominant inheritance (62%), and the

genes that most often showed variation were *NOTCH3* Z (n = 13), *SPG7* (n = 11) and *RFC1* (n = 8). The authors concluded that ES-based molecular testing can be successfully and efficiently used to diagnose adult-onset neurologic diseases but point out some technological limitations and recommend further studies assessing other technologies (such as genome sequencing) that could be used to assist with diagnosis of rare neurological diseases.

In a prospective, multicenter study to evaluate clinical utility and diagnostic yield of a targeted gene panel for inherited neuromuscular disorders (INMD), Barbosa-Gouveia et al. (2022) used comprehensive gene-panel analysis and next-generation sequencing (NGS) to evaluate 268 patients (both pediatric and adult) with a suspected diagnosis of INMD. Three versions of the multi-gene testing panel were designed during the three year study period, with progressive addition of genes to the panel, resulting in an exponential increase in diagnosis rate. The first version (278 genes) yielded a diagnosis rate of 31% while the third (324 genes) yielded a diagnosis rate of 40%. Mean diagnostic rate over the entire 3 year study period was 36%. Most common diagnoses included 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 assert that in the case of INMDs, reaching a definitive diagnosis requires identification of specific variants in disease-causing genes. They recommend comprehensive gene-panel testing of all neuromuscular disease-related genes, including those most commonly implicated, in individuals with suspected INMD.

In a 2021 publication, Nicolau et al. discussed approaches for genetic testing of muscle and neuromuscular junction disorders. The authors indicate that the patient's phenotype sets the guiding approach for genetic testing. Phenotypes suggesting myopathy that require targeted testing (i.e., myotonic dystrophies, FSHD, OPMD, OPDM, DMD and mitochondrial myopathies) must be identified as a first step. For remaining patients, the researchers suggest a gene panel encompassing a large number of genes related to congenital myasthenic syndromes (CMSs) and myopathies, including copy number variation analysis. Specific focus should be placed on the avoidance of missing potentially treatable neuromuscular conditions such as Pompe disease or CMSs. Unfortunately, according to this article, many patients will remain without molecular diagnosis even after testing due to such factors as disorders not amenable to detection via NGS or acquired disorders mimicking inherited myopathies. The researchers state that techniques including exome, genome and RNA sequencing will likely play a greater role in the investigation of undiagnosed patients in the near future.

Bowen et al. (2021) reported the clinical findings of a no-charge, sponsored NGS program called "SMA Identified". Eligible individuals had either a confirmed or suspected diagnosis of spinal muscular atrophy (SMA), or a family history of SMA. The study took place over a 2 year period. A total of 2,459 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 uncertain significance [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 with or at higher risk for SMA may lead to earlier interventions in individuals with SMA.

Winder et al. (2020) aimed to demonstrate the clinical utility of genetic testing by creating a comprehensive data set by analyzing 25,356 unrelated individuals after testing with 266 genes using NGS. The panel was designed using published literature and genotype-phenotype associations. The patients were enrolled in the study if there was a suspicion of NMD and from the study, a definitive diagnosis was determined in 5,055 (20%) of the patients. Usual genetic studies do not routinely include copy number variation (CNV) analysis; however, in this study, the CNVs account for 39% of the significant variants found. Multi-gene testing addressed differential diagnoses in at least 6% of individuals with positive results.

Westra et al. (2019) used WES for a NMD population with both children and adults. A cohort of 396 patients was analyzed by clinical exome sequencing and then diagnostic interpretation of variants. Significant variants were found in 75/396 patients (19%). Variants in the three COL6-genes were identified as the most common cause of the NMD followed by variants in the *RYR1* gene (in total 25% of cases). Likely pathogenic variants and/or variants of uncertain significance were identified in 95 of the patients (24%).

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As part of the North Carolina Clinical Genomic Evaluation by Next-Generation Exome Sequencing Study (NCGENES), Haskell et al. (2018) used WES to determine a genetic diagnosis in 93 patients with NMD. Patients were categorized into three groups based on clinical findings; primarily neuropathy, primarily myopathy, or complex. After DNA extraction and WES, variants were filtered through three different gene lists in order to compare diagnostic yield between different lists. A neuropathy list of 199 genes implicated in neuropathy phenotypes, a myopathy list of 181 genes, and a list of 482 genes implicated in NMD were used. Variants were then categorized using the American College of Medical Genetics and Genomics (ACMG) standards on pathogenicity. The overall diagnostic yield of WES for pathogenic or likely pathogenetic variants was 12.9%, and each gene list gave a different diagnostic yield. In some cases, family testing was performed to determine gene segregation and verify pathogenicity. The authors found that in patients with a clear neuropathy or myopathy, WES had the same diagnostic yield as the broader diagnostic test list. In patients with a complex phenotype, the broader list had the best diagnostic yield (9%) when compared to the neuropathy (4.9%) or myopathy (0%) diagnostic lists. Many of these patients had undergone muscle biopsy (42%), nerve conduction studies or electromyograms (86%), and genetic testing previously (68% overall and 20% had a multi-gene panel) and a definitive diagnosis had not been reached. The participants biopsy, electrodiagnostic testing, and prior genetic results were reviewed by three independent specialist reviewers who categorized the testing as informative or noninformative in the context of WES results. Sixty-three percent of the prior testing was considered informative, meaning that it correlated with the pathogenic variant identified in WES as a neuropathy, myopathy, or a complex disorder. In two cases, WES identified molecular diagnoses that directly impacted medical treatment. One patient had been clinically diagnosed with a chronic inflammatory demyelinating polyneuropathy, but WES demonstrated that the genetic diagnosis of Spastic Ataxia of Charlevoix-Saguenay, so unnecessary immunotherapy was avoided. The second patient had been thought to have a hereditary spastic paraplegia, but the genetic diagnosis was confirmed as a form of dopa-responsive dystonia, and after dopa therapy was started, she regained the ability to walk without assistance. The authors concluded that introducing genome-scale sequencing into the clinical workflow earlier may shorten the diagnostic odyssey, minimize invasive testing, and provide potential opportunities for clinical and investigational therapeutics for patients with NMD.

Wu et al. (2018) evaluated a group of 169 patients referred to a Canadian neuromuscular clinic with an NGS panel of 163-183 neuromuscular disease related genes. Patients included in the study had unexplained hyperCKemia and had a CK value recorded more than 3X the usual upper limit. Patients were excluded if they were suspected of having an acquired or inflammatory cause for their symptoms like a statin induced myopathy, or had classic features of a single gene NMD, such as myotonic dystrophy or Duchenne muscular dystrophy. The ACMG guidelines were used to interpret variants, and variants identified in patients before the publication of the ACMG guidelines underwent re-interpretation in 2017. Pathogenic and likely pathogenic variants were considered in the calculation of the detection rate. Overall, pathogenic and likely pathogenetic variants were identified in 61 (36%) of patients. In the cohort that presented with muscle weakness (n = 135), causative variants were found in 50 (37%). The detection rate in only pediatric patients (n = 47) was 38%. In individuals with recurrent rhabdomyolysis (n = 18), causative variants were found in six (33%). Sixteen patients had idiopathic hyperCKemia, and five (31%) had candidate variants identified. The authors noted that clinicians should be aware of the limitations of NGS testing, and that clinical examination and other diagnostic tools such as electromyography and muscle biopsy are still an important part of the diagnostic process. NGS may be subject to laboratory-specific limitations in detecting a variety of variant types including copy number variants, regulatory sequence variants, trinucleotide repeat expansions, and deep intronic mutations.

Nishikawa et al. (2017) studied the clinical utility of targeted NGS panels designed to identify inherited muscle diseases associated with muscular dystrophy, congenital myopathy (CM), metabolic myopathy (MM), and myopathy with protein aggregations/rimmed vacuoles (MFM). They analyzed blood samples on 188 patients who had blood and muscle biopsy submitted to their lab in 2014 and 2015. Genes for the panels were identified from the 2013 gene table of monogenic NMD, and the target gene numbers were 65 (muscular dystrophy), 41 (CM), 45 (MM), and 36 (MFM). The authors did not combine the genes into one large panel for cost and time efficiency purposes. To analyze the muscular dystrophy panel, 65 patients were recruited who had muscle biopsies and clinical findings suspicious for muscular dystrophy. Likely causative mutations were found in 30 patients (46%), and the genotype correlated with clinical findings. Sixty-five patients were analyzed for the CM panel. Causative mutations were found in 17 patients (26%), and an additional 13 patients had variants that were consistent with their phenotype, but not enough data existed in the literature to be able to designate the mutations as pathogenic. Ten patients were analyzed for the MM panel (30%). Causative mutations were found in three patients. The MFM panel was evaluated in 48 patients who had histological profiles in biopsied muscle tissue consistent with MFM. Causative mutations were found in 12

patients (25%). Overall, the diagnostic yield was 33% for all 188 patients. The authors noted that additional genes and data that might have changed some variant classifications were found after the analysis was complete, so panels need to be updated on an ongoing basis. Their final conclusion was that a NGS panel in combination with histological, mRNA, and protein analysis is useful and efficient for determining a genetic diagnosis in patients with muscle disease.

Five hundred and four patients and eighty-four family members from the Italian Network of Congenital Myopathies and the Italian Network of Limb-Girdle Muscular Dystrophy were studied by Savarese et al. (2016) using an NGS platform designated MotorPlex. MotorPlex is made up of 93 genes that are considered causes of nonsyndromic myopathies that typically cannot be diagnosed clinically. Eighty-five percent of the patients were Italian, and 60% were male. All patients were classified according to their primary clinical presentation as LGMD (51%), congenital myopathy (CM) (32%), distal myopathy (3.8%), isolated hyperCKemia (3.4%), metabolic myopathy (MM) (1.2%), or other (8.6%). Most cases were sporadic, but 96 were familial. Bioinformatic filters took into account population frequency and current variant annotation. Variants were further scrutinized based on clinical presentation, age of onset, and segregation analysis in family members when appropriate. As a result, 218 (43.3%) cases obtained a diagnosis, and 160 patients had candidate variants identified that were interesting, but unproven. LGMD genes were responsible in 115 patients. In 30% of diagnosed cases the phenotype was atypical for that gene, expanding the understanding of the disease phenotype. The authors noted that some of the unsolved cases could be due to variants in genes not yet identified as causing NMD, and that ancillary tests such as comparative genomic hybridization (CGH) to detect copy number variants may be a necessary subsequent step. The conclusion of the study was that next generation sequencing (NGS) may become a universal first tier step in diagnosing heterogeneous conditions such as NMD.

Clinical Practice Guidelines

American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM)

AANEM developed a position statement regarding the utility of genetic testing in neuromuscular disease (NMD) (Kassardjian et al. 2016). The goal of the statement was to generally endorse genetic testing as a component of diagnosing NMD, 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 that included 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 note that recommendations and guidelines exist that direct the selection of appropriate genetic tests and referenced AANEM guidelines for limb-girdle muscular dystrophies (Narayanaswami et al. 2014; reaffirmed 2022), congenital muscular dystrophy (Kang et al. 2015; reaffirmed 2021) and facioscapulohumeral muscular dystrophy (Tawil et al. 2015; reaffirmed 2021).

Metabolic Myopathies

Metabolic refers to the chemical processes in the body that utilize nutrients and energy to provide healthy functioning and growth. Metabolic myopathies are genetic disorders in which the metabolic processes for the muscles have been interrupted and can result in muscle weakness, exercise intolerance, or muscle pain. There are three primary categories of metabolic myopathies that include glycogen-storage diseases (GSD), disorders of fatty oxidation, and mitochondrial myopathies (American College of Rheumatology, 2023 and Tarnopolsky, 2016).

Glycogen Storage Diseases

Glycogen storage diseases (GSDs) that may cause metabolic myopathies and have overlapping symptoms include GSD type 2 (Pompe disease), GSD type 3 (Debrancher Deficiency), GSD type 4 (Andersen's disease), GSD type 5 (McArdle's disease), GSD type 7 (Tarui disease), and GSD type 9 (Phosphorylase Kinase Deficiency). Glycogen storage diseases (GSDs) that may cause metabolic myopathies and have overlapping symptoms include GSD type 2 (Pompe's disease), GSD type 3 (Debrancher Deficiency), GSD type 4 (Andersen's disease), GSD type 5 (McArdle's disease), GSD type 7 (Tarui's disease), and GSD type 9 (Phosphorylase Kinase Deficiency). Identifying the correct diagnosis is important because some GSDs have treatment available, such as Late Onset Pompe Disease (Lilleker et al., 2018). Symptoms often start in the second or third decade of life with muscle cramps that occur during the first few minutes of exercise. Many individuals may not see their physician at the onset of symptoms because they avoid exercise or they modify exercise by starting off slow, then ramping up activity as aerobic metabolism takes over and blood born energy is delivered to the muscle. In particular, individuals with McArdle disease report that exercise gets easier after a few minutes of activity, known as the second wind-phenomenon, and feel better and less symptomatic after a high carbohydrate meal. Patients with other forms of metabolic myopathies do not experience a second wind phenomenon and report that they feel worse with a high carbohydrate meal and better after fasting. Some patients will experience dark urine due to the presence of muscle derived proteins. The classic diagnostic test is a forearm exercise test

included pre-and post-exercise measurements of lactic acid and ammonia. This has a very high sensitivity and specificity for the presence of a glycogenic defect, with the possible exception of phosphorylase b kinase deficiency, which can be further evaluated with an aerobic cycling test. Serum CK is usually elevated in McArdle disease, but is typically normal in other glycogen storage diseases. EMG is often normal, and muscle biopsy may show high glycogen, absent phosphorylase, or absent phosphofructokinase. If these tests suggest McArdle syndrome, or muscle biopsy is suggestive of a particular GSD, targeted genetic testing is suggested to confirm the diagnosis. For example, on muscle biopsy, central cores suggest *RYR1* or *CACNA1S* mutations, abnormal dystrophin staining suggests a dystrophinopathy, ragged red fibers point to a mitochondrial disorder, and membrane bound glycogen suggests Pompe disease. Otherwise, NGS panels may be beneficial in reaching a diagnosis (Lilleker et al., 2018 and Tarnopolsky, 2016).

Sniderman King et al. (2023) reported on data from the Lantern Project, a program offering diagnostic assistance to individuals with suspected Pompe disease and LGMD as well as other lysosomal storage and neuromuscular disorders. Included in this article was information specific to an acid α-glucosidase (GAA) enzyme assay as well as *GAA* sequencing and lastly, the Focused Neuromuscular Panel, which includes *GAA*. A total of 140 individuals in the project have been confirmed to have Pompe disease. The most common symptom reported at the time of testing was proximal muscle weakness (58 individuals) and elevated creatinine kinase (29 individuals) was the most common laboratory result. Molecular results supported diagnosis in 128 individuals. The authors assert that these findings further support the use of testing with enzymatic and genetic methods to aid in the diagnosis of Pompe disease and indicate that the use of multigene NGS panels allow the critical differentiation between Pompe disease and other LGMDs.

Johnson et al. (2017) utilized WES to determine the diagnostic yield of this technology for identifying LOPD in a cohort of 606 European patients with limb-girdle weakness. Their ages ranges from 4 to 88 years old and were 46% female and 56% male. WES from blood was performed by the Genomics Platform at the Broad Institute of Harvard and MIT, and variants were filtered using a list of 169 genes associated with limb-girdle weakness. The biological relevance of the variants identified within the *GAA* gene was determined by considering the population frequency, deleteriousness of the variant predicted by various bioinformatics tools, ClinVar reports of pathogenicity and the published literature. The authors reported that the overall diagnostic rate for all muscle disease was still under review at the time of publication but appeared to be 49% overall. Twelve cases of LOPD were identified in this study, in eight study participants and four siblings. Four of the ten gene variants found had not been reported previously. The authors noted that *GAA* activity levels are typically analyzed using dried blood spot analysis, but for the subset of patients with elevated creatinine kinase and limb-girdle muscle weakness, the testing was not accurate. Nearly 8% had abnormal *GAA* activity levels, but only 2.4% were confirmed to have LOPD. They also highlighted one case of a woman with symptom onset in her fifties who had normal, but slightly lower *GAA* activity on dried blood spot, but was found to have two known pathogenic *GAA* mutations. The authors concluded that NGS was beneficial in the diagnosis of LOPD and has the potential for earlier diagnosis and treatment over current approaches.

Mori et al. (2017) examined the analytical and clinical validity of WES for identifying early and late onset Pompe disease. The disease is treatable by enzyme replacement therapy, but optimal outcomes are dependent on a swift and accurate diagnosis, which is challenging in the late onset form. The authors analyzed WES data in 93 patients with confirmed Pompe disease and known *GAA* mutations identified by Sanger sequencing. WES accurately identified both *GAA* variants in 77 (83%) of patients. One variant was missed in 14 (15%) and both were missed in two (2%). One patient had a complex indel that was incorrectly identified by WES due to misalignment. The authors concluded that WES may not be the most accurate approach to diagnosing Pompe disease, and clinicians should consider more targeted and specific testing in individuals with myopathy, respiratory failure, or other subtle symptoms.

The genetic lab at Centro de Diagnóstico de Enfermedades Moleculares in Madrid, Spain, reported on its experience with NGS for GSD (Vega et al., 2016). Blood samples from 47 patients suspected of having a GSD were analyzed. Two methods were employed. Sixteen patients were analyzed using a panel of 111 GSD related genes. Twelve of these patients, plus an additional 39, were analyzed by the TrueSightOne gene panel which represents all of the known disease-causing genes described in the Online Inheritance of Man (OMIM) database as of 2013. Variants were filtered by population frequency, phenotype, and inheritance pattern. Genes with potentially pathogenic mutations were assessed in the context of the patient phenotype according to OMIM criteria. Variants that met these criteria were confirmed by Sanger sequencing. In the first testing group, five of 12 patients received a genetic diagnosis (30%). In the second group, 18 of 43 patients were found to have pathogenic mutations. Fourteen were in GSD related genes and four in non-GSD genes. Eleven mutations had never been reported before and were confirmed through segregation analysis. The authors concluded that the combination of clinical findings, biochemical test results, and NGS can provide an efficient and accurate means of making a genetic diagnosis.

Lévesque et al. (2016) studied the clinical utility of a targeted NGS panel to diagnose Late Onset Pompe Disease (LOPD). Pompe disease is an autosomal recessive disease caused by a defect in the *GAA* gene, resulting in a deficiency of acid alpha-glucosidase. The classic infantile form presents early in life with general muscle weakness, cardiomyopathy, and respiratory distress. The disease is treatable with enzyme replacement therapy, but without treatment, it is a fatal disease. LOPD can present at any age after infancy with limb-girdle weakness but is most commonly identified in adulthood. Patients can also have rigid spine syndrome, scoliosis and low body mass, and nocturnal hypoventilation due to diaphragmatic weakness. Because of the low incidence of LOPD and the overlap of symptoms with other neuromuscular disease, this treatable condition is often not diagnosed until 10 years after the first onset of symptoms. The authors developed a NGS panel comprised of 77 genes representing muscle disorders with a clinical overlap with LOPD. Twenty Pompe patients with known mutations were used to determine the sensitivity of the assay, and all mutations were accurately identified. Positive gene results were confirmed by measuring *GAA* activity. *GAA* activity level was measured using tandem mass spectrometry, and 15 Pompe patients were used as positive quality controls and 49 healthy controls were used to establish normal *GAA* activity. This pilot study included 34 patients suspected of having an inherited muscle disorder, but in whom the etiology could not be determined. Seven pediatric patients and 27 adult patients were included. Most (71%) had undergone a muscle biopsy, and 15 (44%) had at least one single gene test performed, but still did not have a diagnosis. Using the NGS panel, a genetic diagnosis was found in 32% of patients. One case of LOPD was found, confirmed by *GAA* activity testing. The remaining cases were various forms of LGMD, including three patients with atypical presentations. The authors concluded that targeted muscle gene panels utilized as a first-tier diagnostic test might reduce the time to diagnosis. They also note that challenges exist with the high number of VUS identified and the limited performance of bioinformatics tools for analyzing copy number variants but anticipate that these issues will be resolved as NGS technology continues to advance.

Savarese et al. (2016) described the clinical validity of a targeted NGS panel (MotorPlex) for NMD in 504 patients with Limb Girdle Muscular Dystrophy (LGMD) (51%), congenital myopathy (CM) (32%), distal myopathy (3.8%), isolated hyperCKemia (3.4%), and metabolic myopathy (MM) (1.2%) and other (8.6%). Within this subset of patients are 275 individuals with a clinical presentation of LGMD and hyperCKemia that includes LOPD within the differential diagnosis reported in a subsequent publication focusing on LOPD (Savarese et al., 2018). Ultimately, 16 patients from nine unrelated families were diagnosed with LOPD. All patients had the common c. 32 13T > G variant in the *GAA* gene with a second, already known mutation on the other allele. The symptoms in this cohort were primarily proximal weakness and fatigability. Exercise intolerance, myalgia, and contractures were less common. Some patients had atypical symptoms that likely confounded the clinical diagnosis, such as dysphagia, pseudohypertrophy, and calf hypertrophy. The authors concluded that with decreasing costs and technological improvements, NGS panels are likely to become important in first tier diagnostic testing in the near future.

Limb Girdle Muscular Dystrophies (LGMD) and Myofibrillar Myopathies (MFM)

LGMD are a relatively rare group of diseases impacting up to .43 per 100,000 individuals. Incidence can vary by ethnicity (Narayanaswami et al., 2014; reaffirmed 2022). LGMD are characterized by proximal muscle weakness (shoulders, upper arms, pelvic area, and thighs), muscle wasting, and myopathic or dystrophic myopathological features (Kuhn et al., 2016). There are many subtypes of LGMD which can vary with age of onset, severity, and additional co-morbidities such as weakness of the heart muscles (MedlinePlus, 2019). There are at least thirty genes associated with LGMD; seven are autosomal dominant, and twenty-three are autosomal recessive (Kuhn et al., 2016). LGMD are classified according to inheritance pattern. LGMD1 are autosomal dominant, and LGMD2 are recessive. Further subtyping is delineated using a letter. In their most recent guidelines, the American Academy of Neurology (AAN) identified LGMD1A-LGMD1F, and LGMD2A-LGMD2S (Narayanaswami et al., 2014; reaffirmed 2022).

In a retrospective evaluation, Çavdarlı et al. (2023) assessed the diagnostic rate of a 47-gene, NGS-based panel (created by the research team) to identify genetic variations in a population of 146 individuals in Turkey (ages 6 months to 67 years) suspected to have a neuromuscular disorder based on clinical examination, laboratory findings and imaging. Individuals who had been diagnosed with dystrophinopathy based on genetic evaluation of dystrophin by MLPA were excluded. The genes included in the panel targeted variations related to muscular dystrophy and myopathies that have been suggested for first-tier testing. Based on the study results, 67 individuals were found to have a genetic basis for their disorder, correlating to a diagnostic yield of 46%. Twenty-three genes showed variations associated with neuromuscular disorders; these included *CAPN3(11), DYSF(9), DMD(8), SGCA(5), TTN(4), LAMA2(3), LMNA(3), SGCB(3), COL6A1(3), DES (2), CAV3(2), FKRP(2), FKTN(2), 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 those with VUS, only one heterozygous variant for an autosomal recessive disease and individuals with two variants in different genes. Based on the results of the study, the authors assert that

targeted NGS testing is a viable option for molecular diagnosis of neuromuscular conditions such as muscular dystrophy and could reduce the need for WES.

Winckler et al. (2022) examined the diagnostic yield of an NGS panel made up of 39 genes to be used as a first-tier test for diagnosing individuals with genetic myopathies. This cross-sectional study took place in Brazil and included 51 cases where genetic myopathies were suspected based on clinical findings. In this study, the diagnostic yield of the NGS panel was found to be 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%), 7/14 individuals (50%) with congenital muscular diseases were identified and 7/10 (70%) with muscular dystrophy including prominent joint contractures. The researchers indicate that these results show that the customized NGS panel studied produced high diagnostic yields when used early in the exploration of gene-related myopathies, which could result in earlier diagnosis and potential treatments.

Töpf et al. (2020) established an international consortium, MYO-SEQ, aiming to aid in the workups and improve the diagnostic pathway for patients with limb-girdle muscle diseases and better understand the etiology of these rare diseases. The authors note that gene-by-gene and small panel testing strategies are typically dictated by phenotype, which leaves little room for the expansion of disease associations and new disease characterizations, and that NGS technologies have been integral in the diagnosis of some of the 955 distinctNMD. As of publishing date, 535 genes are known to be associated with these disorders. The researchers applied a sequential targeted exome sequencing to a large cohort of 1001 undiagnosed patients with proximal muscle weakness and/or elevated serum creatine kinase. Exomes were analyzed for variants in 429 genes that are associated with muscle conditions. Suspected pathogen variants were found in 52% of patients across 87 genes. Four-hundred one novel variants were detected and 116 of these were recurrent. Variants in CAPN3, DYSF, ANO5, DMD, RYR1, TTN, COL6A2, and SGCA together made up over half of the solved cases. Variants in newer disease genes, such as BVES and POGLUT1, were also found. The authors concluded that their data suggest exome sequencing as an appropriate method for pathogenic variant detection in patients where genetic muscle disease is suspected, focusing first on common disease genes and subsequently in rarer or newly characterized genes.

In the United Kingdom, individuals suspected to have LGMD are evaluated at a central clinical known as the UK LGMD clinic. Harris et al. (2017) reported that in this population a genetic diagnosis is achieved in 63% of patients using standard clinical approaches, and her team explored the use of WES to increase the diagnostic yield in the remaining third of patients. They examined 104 affected individuals from 75 families. Patients had already undergone targeted genetic testing with an average of eight genes screened, as well as other extensive clinical investigations such as muscle biopsy and electrodiagnostic testing. In some cases, the ongoing clinical analysis had taken place over a decade or longer without reaching a definitive diagnosis. The WES genetic variants were filtered and analyzed against a list of known muscle disease genes, and if no variants were found, the scope of variant analysis was widened to include variants in novel genes. The genetic findings, clinical features, muscle MRI and muscle biopsy results were then integrated at a multidisciplinary meeting to reach a consensus as to whether variants were likely to be disease causing. Overall, the WES group achieved a diagnostic yield of 37%. By comparison, 91 individuals from 84 families were tested using the standard genetic testing procedures in place in the clinic during the 24-month investigation period. This standard genetic testing group had a diagnostic yield of 33%. The authors concluded that earlier application of WES in the diagnostic pathway would reduce the time to diagnosis and may also reduce the costs incurred by ongoing investigations, as well as affording opportunities for detection of low-level mosaicism and novel disease gene identification.

Kuhn et al. (2016) examined the clinical utility of a NGS panel for LGMD in a group of fifty-eight German patients who were suspected to have a LGMD. The panel focused on 23 genes known to cause LGMD and 15 genes known to cause a similar phenotype. The age of onset ranged from 3 to 63 years of age. Four patients had autosomal dominant forms of disease, and sixteen patients had affected siblings, suggesting autosomal recessive. X-linked inheritance was most likely in two patients. The remaining patients were considered to have sporadic cases. All patients had a muscle biopsy that confirmed myopathic or dystrophic changes, but LGMD immunohistochemistry or immunoblotting was not possible on the remaining sample. NGS was performed on the 38 targeted genes with an average 20X coverage. All pathogenic variants and VUS were confirmed by Sanger sequencing. Disease causing mutations that explained the phenotype were found in 19 of 58 patients (33%). In 28% of patients with autosomal recessive disease, only a single pathogenic mutation was found. Additional sequencing and copy number variant analysis on the relevant gene to identify another pathogenic mutation, consistent with recessive inheritance, was negative. VUS were found in 10% of patients, and the remainder had no mutations identified.

Monies et al. (2016) studied a NGS panel of 759 genes associated with neurological disorders in patients from 50 families presenting with muscle weakness affecting the pelvic girdle and shoulder, of which 36 had an autosomal recessive form of

inheritance. These families were identified through the Neurosciences Clinic of King Faisal Specialist Hospital and Research Centre, Saudi Arabia. Variants were analyzed and classified using the ACMG and AMP guidelines. Thirty-eight families (76%) received a genetic diagnosis from this study. Thirty-four had LGMD related mutations, and four had novel genetic variants not usually associated with LGMD. Families with negative results had follow up WES, but no additional variants were found. The authors concluded that their panel was sensitive, cost-effective, and rapid; significantly assisting the clinical practice.

Ankala et al. (2015) reported on the design and validation of several NGS panels at Emory Genetics Lab (EGL), developed to help expedite the diagnosis of NMD, including LGMD. The authors report that in their experience, clinicians must go through an extensive diagnostic workup in order to determine a small gene list to pursue for NMD, and patients may opt out of the process before a diagnosis is finalized. A combination of a targeted NGS panel and a targeted CGH test to identify copy number variants may reduce the burden of invasive tests. From October 2009 to May 2014, the authors analyzed the data for LGMD single gene and NGS/CGH panels to determine the difference in clinical utility. Exome analysis was also compared for 20 random patients to determine how well the exome covered the NMD genes in the study. In this timeframe, 343 LGMD single gene tests were ordered which included 250 sequencing tests and 93 CGH tests. The diagnostic yield was 19% overall. It was very low for CGH, with only eight positives of 93 tested. Ninety-six patients had a LGMD eleven gene NGS panel with a diagnostic yield of 26%. Eighty-one patients had a broad NGS panel that covered 41 genes for NMD, including genes that can cause overlapping phenotypes with LGMD, Emery-Dreifuss muscular dystrophy (EDMD), metabolic myopathies, congenital myopathies, dystrophanopathies, and congenital disorders of glycosylation (CDG). The diagnostic yield of the NMD panel was 46%. The authors also compared WES to the LGMD and NMD panel. Based on the low coverage of WES for some key NMD genes, they concluded that WES would miss variants in five key LGMD genes, whereas the NMD panel would miss one.

Clinical Practice Guidelines

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

When presented with a patient with a possible LGMD or other distal myopathies like MFM, the AAN and AANEM (Narayanaswami et al., 2014, reaffirmed 2022) recommend referring patients to a specialized neuromuscular center for evaluation, management, and diagnosis because of the complex nature of NMDs and the need for a multi-disciplinary team. They recommend utilizing an approach focused on a clinical evaluation to narrow down the possible forms of LGMD or other muscular dystrophies. Their evidence-based review found that utilizing information such as pattern of muscle weakness, hypertrophy, or atrophy of certain muscle groups, cardiac or respiratory involvement, muscle biopsy findings, electromyogram (EMG) results, and creatinine kinase (CK) serum levels, can narrow down the differential to just a few disorders. Verification of the specific disorder through genetic testing is recommended, as this will direct the most efficient care path and identify necessary prophylactic interventions, such as the correct timing for placing a pacemaker, or the monitoring interval for cardiorespiratory function.

The following phenotype and genotyping recommendations (evidence level B, expert consensus based on moderate evidence) were provided for those with limb girdle weakness and probable autosomal dominant inheritance:

- If cardiomyopathy, respiratory involvement, EMG with myotonic or “pseudomyotonic” discharges, foot drop, and myofibrillar myopathy on muscle biopsy are present; test for mutations in the genes desmin (LGMD1E), myotilin (LGMD1A), DNAJB6 (LGMD1D), ZASP, filamin C, αB-crystallin, and titin.
- If rippling muscles and percussion-induced rapid contractions are present; test for mutations in the caveolin-3 gene (LGMD1C).
- If early humeroperoneal weakness, contractures (neck, elbows, knee, ankle), and cardiomyopathy are present; test for mutations in the lamin A/C gene (LGMD1B or AD-EDMD).
- If distal weakness, myotonic discharges on EMG, past or family history of Paget disease, frontotemporal dementia, or motor neuron disease are present; test for mutations in VCP (hIBMPFD).
- If no clinical features suggest a specific form of dystrophy, or if initial genetic testing is not informative, perform a muscle biopsy to direct further genetic testing (such as immunohistochemistry/immunoblotting for various sarcolemmal proteins, calpain-3, or features of myofibrillar myopathy) or to exclude an alternative diagnosis (e.g., a metabolic myopathy, mitochondrial myopathy, congenital myopathy, or inflammatory myopathy).

The following phenotype and genotyping recommendations (evidence level B, expert consensus based on moderate evidence) were provided for those with limb girdle weakness and probable autosomal recessive inheritance:

- If scapular winging but no calf hypertrophy, and normal cardiorespiratory function are present; test for mutations in calpain-3 (LGMD2A). Patients of English, French, Spanish, Italian, Portuguese, or Brazilian descent may have a higher pretest probability of this disorder.
- If calf atrophy and weakness (i.e., inability to stand on toes) are present; test for mutations in anoctamin-5 (LGMD2L) or dysferlin (LGMD2B).
- If the onset of symptoms is in the teens or early twenties or the patient is from Asia, clinicians should assess for dysferlin mutations first and, if negative, test for anoctamin-5 mutations. If the onset of symptoms is in the 30s or later or the patient is of English or northern European ancestry, clinicians should assess for anoctamin-5 mutations first and, if negative, test for dysferlin mutations.
- If muscle biopsy immunohistochemistry showing reduction in 90 α-, β-, γ-, or δ-sarcoglycans is present; test for mutations in the sarcoglycan genes, SGCA, SGCB, SGCG, and SGCD (LGMD2C–2F).
- If the patient is of Hutterite descent; test for mutations in TRIM32.
- If scapular winging, calf hypertrophy, and early cardiorespiratory involvement are present; test for mutations in *FKRP*.
- If mental retardation is present; test for mutations in genes that cause primary or secondary deficiency of α-dystroglycan, POMT1, POMT2, FKTN, FKRP, LARGE1, POMGNT1, and ISPDI genes (LGMD2K, LGMD2M, LGMD2N, LGMD2O, and LGMD2P).
- If epidermolysis bullosa or pyloric atresia; test for mutations in plectin, PLEC.

If no other specific clinical features are identified, or the muscle biopsy does not inform genetic testing, clinicians should perform a dried blood spot test for α-glucosidase (acid maltase) deficiency or Pompe disease.

The following phenotype and genotyping recommendations (evidence level B, expert consensus based on moderate evidence) were provided for those with limb girdle weakness and probable X-linked inheritance:
- If male, perform testing for mutations in the dystrophin (DMD) gene.
- If female, test for *DMD* gene mutations or perform a muscle biopsy and immunostaining for dystrophin to assess for a mosaic pattern of staining. If positive, confirm diagnosis with DMD gene testing.

The following phenotype and genotyping recommendations (evidence level B, expert consensus based on moderate evidence) were provided for those with humeroperoneal weakness and probable autosomal dominant inheritance:
- If early cardiac involvement and no joint laxity are present; perform genetic testing for mutations in the lamin A/C gene (AD-EDMD, LGMD1B).
- If joint laxity, protuberant calcaneus, and no cardiac involvement are present; test for mutations in the collagen VI gene (Bethlem myopathy).

The following phenotype and genotyping recommendations (evidence level B, expert consensus based on moderate evidence) were provided for those with humeroperoneal weakness and probable autosomal recessive inheritance:
- If congenital onset, joint laxity, protuberant calcaneus, and no cardiac involvement are present; test for mutations in the collagen VI gene (Ullrich myopathy).

The following phenotype and genotyping recommendations (evidence level B, expert consensus based on moderate evidence) were provided for those with humeroperoneal weakness and probable X-linked inheritance:
- If joint laxity, protuberant calcaneus, and no cardiac involvement are present; test for mutations in the emerin (EMD) gene.

If humeroperoneal weakness and suspected muscular dystrophy with early cardiac involvement and no joint laxity are present, and there are no mutations found in the lamin A/C or emerin gene, clinicians should perform muscle biopsy to delineate characteristic abnormalities that direct further genetic testing (evidence level B, expert consensus based on moderate evidence).

If late adult onset of index finger and wrist extensor weakness, followed by atrophy and weakness of hand muscles, and muscle biopsy showing rimmed vacuoles are present; a diagnosis of Welander distal myopathy is most likely and should be confirmed through genetic testing for Welander myopathy (evidence level B, expert consensus based on moderate evidence).

The following phenotype and genotyping recommendations (evidence level B, expert consensus based on moderate evidence) were made for patients with suspected distal muscular dystrophy and probable autosomal recessive inheritance:
- If early onset of calf weakness is present; test for mutations in the anoctamin-5 and dysferlin genes.

- If early onset (< 30 years of age) of progressive foot drop is present in individuals who are of Japanese or Middle Eastern Jewish descent; test for GNE mutations (AR-hIBM).
- If none of the clinical features above are noted, clinicians should perform a muscle biopsy to direct further genetic testing.

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 EMG) and biopsy features (myofibrillar myopathy [MFM], reduction of emerin immunostaining, presence of rimmed vacuoles) to guide genetic testing, which may include mutations in the genes causing the various forms of MFM; LGMD2B (dysferlin), LGMD2L (anoctamin-5), LGMD2J (titin), LGMD1C (caveolin-3), and EDMD (emerin and lamin A/C).

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, Whole-Exome Sequencing, Whole-Genome sequencing, or Next-Generation Sequencing to identify the genetic abnormality (Level C, expert consensus based on modest evidence).

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 July 12, 2021)

References

American College of Rheumatology. Metabolic Myopathies. Available at: https://rheumatology.org/patients/metabolic-myopathies. Updated February 2023. Accessed June 20, 2023.

Ankala A, da Silva C, Gualandi F, et al. A comprehensive genomic approach for neuromuscular diseases gives a high diagnostic yield. Ann Neurol. 2015 Feb;77(2):206-14.

Bowen BM, Truty R, Aradhya S, et al. SMA identified: Clinical and molecular findings from a sponsored testing program for spinal muscular atrophy in more than 2,000 individuals. Front Neurol. 2021 May 6;12:663911.

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.

Haskell GT, Adams MC, Fan Z, et al. Diagnostic utility of exome sequencing in the evaluation of neuromuscular disorders. Neurol Genet. 2018 Feb 1;4(1): e212.

Johnson K, Töpf A, Bertoli M, et al. Identification of GAA variants through whole exome sequencing targeted to a cohort of 606 patients with unexplained limb-girdle muscle weakness. Orphanet J Rare Dis. 2017 Nov 17;12(1):173.

Kang PB, Morrison L, Iannaccone ST, et al. Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. 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 & Electrodiagnostic Medicine. Neurology. 2015 Mar 31;84(13):1369-78. Reaffirmed July 2018.

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

Kuhn M, Glaser D, Joshi PR, et al. Utility of a next-generation sequencing-based gene panel investigation in German patients with genetically unclassified limb-girdle muscular dystrophy. J Neurol 2016;263:743–50.

Lévesque S, Auray-Blais C, Gravel E, et al. Diagnosis of late-onset Pompe disease and other muscle disorders by next-generation sequencing. Orphanet J Rare Dis. 2016 Jan 25;11:8.

Lilleker JB, Keh YS, Roncaroli F, et al. Metabolic myopathies: a practical approach. Pract Neurol. 2018 Feb;18(1):14-26.

Monies D, Alhindi HN, Almuhaizea MA, et al. A first-line diagnostic assay for limb-girdle muscular dystrophy and other myopathies. Hum Genomics. 2016 Sep 27;10(1):32.

Mori M, Haskell G, Kazi Z, Zhu X, et al. Sensitivity of whole exome sequencing in detecting infantile- and late-onset Pompe disease. Mol Genet Metab. 2017 Dec;122(4):189-197.

Narayanaswami P, Weiss M, Selcen D. et al; Guideline Development Subcommittee of the American Academy of Neurology; Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Evidence-based guideline summary: diagnosis and treatment of limb-girdle and distal dystrophies: report of the guideline development subcommittee of the American Academy of Neurology and the practice issues review panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology. 2014 Oct 14;83(16):1453-63.

Nicolau S, Milone M, Liewluck T. Guidelines for genetic testing of muscle and neuromuscular junction disorders. Muscle Nerve. 2021 Jun 16. Epub ahead of print.

Nishikawa A, Mitsuhashi S, Miyata N, et al. Targeted massively parallel sequencing and histological assessment of skeletal muscles for the molecular diagnosis of inherited muscle disorders. J Med Genet. 2017 Feb;54(2):104-110.

Ohio Administrative Code/5160/Chapter 5160-1-01. Medicaid medical necessity: definitions and principles. Available at: https://codes.ohio.gov/ohio-administrative-code/rule-5160-1-01. Accessed September 20, 2023.

Savarese M, Di Fruscio G, Torella A, et al. The genetic basis of undiagnosed muscular dystrophies and myopathies: Results from 504 patients. Neurology. 2016 Jul 5;87(1):71-6. Erratum in: Neurology. 2018 Jun 5;90(23):1084. Erratum in: Neurology. 2019 Aug 20;93(8):371.

Savarese M, Torella A, Musumeci O, et al. Targeted gene panel screening is an effective tool to identify undiagnosed late onset Pompe disease. Neuromuscul Disord. 2018 Jul;28(7):586-591.

Schuermans N, Verdin H, Ghijsels J, et al.; for Program for Undiagnosed Rare Diseases (UD-PrOZA). Exome sequencing and multigene panel testing in 1,411 patients With adult-onset neurologic disorders. Neurol Genet. 2023 Apr 26;9(3):e200071.

Sniderman King L, Pan Y, Nallamilli BRR, et al. Pompe disease ascertained through The Lantern Project, 2018-2021: Next-generation sequencing and enzymatic testing to overcome obstacles to diagnosis. Mol Genet Metab. 2023 May;139(1):107565.

Tarnopolsky MA. Metabolic Myopathies. Continuum (Minneap Minn). 2016 Dec;22(6, Muscle and Neuromuscular Junction Disorders):1829-1851.

Tawil R, Kissel JT, Heatwole C, et al. Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Evidence-based guideline summary: Evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology. 2015 Jul 28;85(4):357-64.

Töpf A, Johnson K, Bates A, et al. Sequential targeted exome sequencing of 1001 patients affected by unexplained limb-girdle weakness. Genet Med. 2020 Sep;22(9):1478-1488.

Vega AI, Medrano C, Navarrete R, et al. Molecular diagnosis of glycogen storage disease and disorders with overlapping clinical symptoms by massive parallel sequencing. Genet Med. 2016 Oct;18(10):1037-43.

Westra D, Schouten MI, Stunnenberg BC, et al. Panel-based exome sequencing for neuromuscular disorders as a diagnostic service. J Neuromuscul Dis. 2019;6(2):241-258.

Winder TL, Tan CA, Klemm S, et al. Clinical utility of multigene analysis in over 25,000 patients with neuromuscular disorders. Neurol Genet. 2020 Mar 9;6(2):e412.

Wu L, Brady L, Shoffner J, et al. Next-generation sequencing to diagnose muscular dystrophy, rhabdomyolysis, and hyperckemia. Can J Neurol Sci. 2018 May;45(3):262-268.5:26-32.

Policy History/Revision Information

Date	Summary of Changes
05/01/2024	**Related Policies** • Updated reference link to reflect the current policy title for *Whole Exome and Whole Genome Sequencing (Non-Oncology Conditions) (for Ohio Only)*
01/01/2024	**Application** • Added language to indicate any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using *Ohio Administrative Code 5160-1-01* **Coverage Rationale** • Revised language to indicate: ○ Genetic testing of Neuromuscular Disorders may be covered in certain circumstances; refer to the InterQual® CP: Molecular Diagnostics: ▪ Charcot-Marie-Tooth (CMT) Hereditary Neuropathy ▪ Duchenne Becker Muscular Dystrophy (DBMD) ▪ Glycogen Storage Disease Type I (GSDI) ▪ Niemann-Pick Disease Type A and B ▪ Niemann-Pick Disease Type C ▪ Pompe Disease (Glycogen Storage Disease Type II) ▪ Spinal Muscular Atrophy (SMA) ▪ Whole Genome Sequencing (WGS), Whole Exome Sequencing (WES), and Chromosomal Microarray (CMA) for Congenital or Hereditary Disorders ***Glycogen Storage Disease Type 1 (GSDI) and Pompe Disease (Glycogen Storage Disease Type II)*** ○ Multi-gene panel testing for the diagnosis of Neuromuscular Disorders is proven and medically necessary for suspected glycogen storage disease in: ▪ An adolescent or adult with: – Exercise intolerance, muscle weakness, and muscle cramps; and – Normal or equivocal CK results; and – One of the following conditions is met: • Exercise testing is unavailable or uninformative • Muscle biopsy is unavailable or uninformative • Targeted genetic testing was negative ▪ An infant or child with: – Unexplained liver disease, or muscle weakness, or heart dysfunction; and – One of the following is met: • Muscle biopsy is unavailable or uninformative • Enzyme testing was unavailable or uninformative • Targeted genetic testing was negative **Definitions** • Updated definition of: ○ Whole Exome Sequencing (WES) ○ Whole Genome Sequencing (WGS) **Applicable Codes** • Added CPT codes 0417U and 81448 **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS165OH.D – P

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state (Ohio Administrative Code [OAC]) or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state (OAC) or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state (OAC) or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state (OAC) or contractual requirements for benefit plan coverage. 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.

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