Clinical Features:
Neuromuscular disorders (NMD) are a clinically and genetically diverse group of conditions affecting the peripheral nervous system and muscle, including muscular dystrophies, congenital myopathies and congenital myasthenic syndrome [1]. Most NMDs have an underlying genetic basis, although there are also acquired forms NMD such as botulism and pharmaceutical induced myopathies [1]. Onset of symptoms is variable between different NMD, and can range from prenatal onset to childhood or adult onset conditions. It is becoming increasingly recognized that many genes associated with NMD can lead to multiple disease phenotypes in different families, and some can be associated with both autosomal dominant and recessive inheritance [1].

Our Neuromuscular Disorders Panel includes mutation analysis of all 113 genes listed below.

<table>
<thead>
<tr>
<th>Neuromuscular Disorders Panel</th>
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<tbody>
<tr>
<td>ACTA1</td>
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<tr>
<td>AGRN</td>
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<tr>
<td>ALG14</td>
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<td>ALG2</td>
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<td>ANO5</td>
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<td>B3GALNT2</td>
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<td>B3GNT1</td>
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<td>BAG3</td>
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<td>BIN1</td>
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<td>CAPN3</td>
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<td>CAV3</td>
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<tr>
<td>CCD78</td>
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<td>CFL2</td>
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<td>CHAT</td>
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<td>CHKB</td>
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<td>CHRNA1</td>
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<td>CHRN1</td>
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<td>CHRN2</td>
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<td>CHRN5</td>
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Myopathies

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
<th>Typically Associated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethlem myopathy</td>
<td>Bethlem myopathy (BM) is a variable autosomal dominant condition, associated with proximal muscle weakness and variable contractures. Onset ranges from the prenatal period to adulthood [2].</td>
<td>COL6A1 [2], COL6A2 [2], COL6A3 [2], COL12A1 [3]</td>
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<tr>
<td>Central core disease</td>
<td>Central core disease is characterized by mild to severe muscle weakness and the finding of characteristic cores on muscle biopsy [4]. Most individuals have a milder form of the condition with mild proximal muscle weakness, however more severe forms of the disease with severe infantile hypotonia and respiratory dysfunction have also been reported [4]. Inheritance is typically autosomal dominant, although cases with autosomal recessive inheritance have also been observed.</td>
<td>RYR1 [5]</td>
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<tr>
<td>Condition</td>
<td>Description</td>
<td>Genes</td>
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<tr>
<td>Centronuclear myopathy (CNM)</td>
<td>Centronuclear myopathy (CNM), also known as myotubular myopathy, is a rare muscle disease associated with non-progressive or slowly progressive muscle weakness that can develop from infancy to adulthood [6, 7]. On muscle histopathology, patients with CNM have increased frequency of central nuclei, as well as predominance of type 1 fibers and atrophy, in the absence of other significant abnormalities. Approximately 80% of males with a diagnosis of myotubular myopathy by muscle biopsy will have a mutation in MTM1 identifiable by sequence analysis, which is an X-linked gene. Dominant and recessive forms of CNM also exist.</td>
<td>BIN1 [8], CCDC78 [9], DNM2 [6], MTM1 [10], MYF6 [11], RYR1 [5], SPEG [12]</td>
</tr>
<tr>
<td>Congenital Fiber-type Disproportion</td>
<td>Congenital fiber-type disproportion (CFTD) is a type of congenital myopathy characterized by hypotonia and muscle weakness that varies from mild to severe [13]. The majority of individuals have static weakness. Other features can include feeding difficulties, respiratory failure, ophthalmoplegia, ptosis, contractures and spinal deformities [13]. Histopathologic findings of the condition include type 1 fibers that are at least 12% smaller than type 2 fibers on muscle biopsy. CFTD can be inherited in an autosomal dominant or recessive manner. X-linked inheritance has also been described in some affected families, however the associated gene has not been identified to date.</td>
<td>ACTA1 [14], LMNA [15], MYH7 [16], RYR1 [17], SEPN1 [18], TPM2 [19], TPM3 [20]</td>
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<tr>
<td>Congenital Myopathy - Other</td>
<td>Congenital myopathies are typically characterized by the presence of specific structural and histochemical features on muscle biopsy and clinical presentation can include congenital hypotonia, muscle weakness, delayed motor milestones, feeding difficulties, and facial muscle involvement [21]. Serum creatine kinase may be normal or elevated. Heterogeneity in presenting symptoms can occur even amongst affected members of the same family.</td>
<td>CNTN1 [22], PTPLA [23], RYR1 [5], TTN [24], HRAS [25], MEGF10 [26], STAC3 [27], MYL2 [28]</td>
</tr>
<tr>
<td>Inclusion body myopathy</td>
<td>Inclusion body myopathies are a rare group of disorders with variable clinical presentations, typically including slowly progressive muscle weakness. Findings on muscle biopsy include rimmed vacuoles and collection of cytoplasmic or nuclear 15-21 nm diameter tubulofilaments [29]. Other associated symptoms vary depending on the causative gene, and may also include ophthalmoplegia, Paget’s disease of bone, and frontotemporal dementia [29]. Inheritance may be autosomal dominant or recessive.</td>
<td>GNE [29], VCP [29], MYH2 [29]</td>
</tr>
<tr>
<td>Danon disease</td>
<td>Danon disease is an X-linked dominant condition affecting primarily cardiac muscle. Intellectual disability and skeletal muscle involvement is variable, with men more severely affected than women. Danon disease is thought to be a form of autophagic vacuolar myopathy, characterized by intracytoplasmic autophagic vacuoles with sarcolemmal features [30]</td>
<td>LAMP2 [31]</td>
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<tr>
<td>Laing distal myopathy</td>
<td>Heterozygous mutations in MYH7 have been associated with Laing distal myopathy, which is characterized by weakness in childhood, that initially involves the dorsiflexors of the ankles and great toes, followed by the finger extensors [32].</td>
<td>MYH7 [32]</td>
</tr>
</tbody>
</table>
Marinesco-Sjogren syndrome  | Homozygous or compound heterozygous mutations in *SIL1* are associated with Marinesco-Sjogren syndrome. This condition is characterized by congenital cataracts, myopathy, and delayed psychomotor development. Other features include short stature, hypergonadotropic hypogonadism and skeletal deformities secondary to muscle weakness. | SIL1 [33]  

Multiminicore disease  | The classic form of multiminicore disease (MmD) is associated with hypotonia, delayed motor development, axial muscle weakness and respiratory dysfunction [34]. Onset is typically in infancy or early childhood. Other subtypes of MmD include a moderate form with hand involvement, a severe prenatal form with arthrogryposis, and an ophthalmoplegic form [34]. MmD is typically inherited in an autosomal recessive manner. | RYR1 [5], SEPN1 [34]  

Myofibrillar myopathy  | Myofibrillar myopathy is characterized by slowly progressive muscle weakness that can affect both proximal and distal muscles. Other features may include muscle stiffness and aching, peripheral neuropathy, and cardiomyopathy. EMD can be inherited in an autosomal dominant, autosomal recessive or X-linked manner. | BAG3 [35], CRYAB [35], DES [35], DNAJB6 [36], FHL1 [35, 37], FLNC [35], LDB3 [35], MYOT [35]  

Myopathy with tubular aggregates  | Dominant mutations in *STIM1* and *ORAI1* are related to myopathy with tubular aggregates present in fibers on muscle biopsy. These aggregates represent a non-specific finding occurring in a number of different conditions including late-onset forms of familial myopathy. | ORAI1 [38], STIM1 [39]  

Nemaline myopathy  | Nemaline myopathy is characterized by weakness, hypotonia and depressed or absent deep tendon reflexes. Weakness is typically proximal, diffuse or selective, with or without facial weakness and the diagnostic hallmark is the presence of distinct rod-like inclusions in the sarcoplasm of skeletal muscle fibers [40]. Inheritance may be either autosomal dominant or recessive, and some genes have been observed in association with both inheritance patterns. | ACTA1 [41], CFL2 [42], KBTBD13 [43], NEB [44], LMOD3 [45], TNTT1 [46], TPM2 [19], TPM3 [20], KLHL40 [47], KLHL41 [48]  

### Muscular Dystrophies

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
<th>Typically Associated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital muscular-dystrophy-dystroglycanopathies</td>
<td>Congenital muscular-dystrophy-dystroglycanopathies are a genetically heterogenous group of autosomal recessive conditions. Dystroglycanopathies are characterized by a broad congenital muscular dystrophy phenotypic spectrum with and without intellectual disability, eye involvement and brain findings [49].</td>
<td>DAG1 [50], FKTN [51], FKRP [51], ISPD [51], GMPPB [52], LARGE [51], POMK, POMT1 [51], POMT2 [51], POMGNT1 [51], POMGNT2, TMEM5 [53], B3GALNT2 [54], B3GNT1 [55].</td>
</tr>
<tr>
<td>Congenital muscular dystrophy - Other</td>
<td>Congenital muscular dystrophies are a genetically and clinically heterogeneous group of disorders typically characterized by weakness and dystrophic pattern on muscle biopsy that is present at birth or during the first months of life. Affected infants typically appear 'floppy' and have low muscle tone and poor spontaneous movements [56]. The clinical course is broadly variable [2]. CMDs can be further classified by the mutated gene, the respective protein’s localization and the protein’s predicted function [57].</td>
<td>CHKB [58], DPM2 [59], DPM3 [60], ITGA7 [61], LAMA2 [62], LMNA [51], SEPN1 [51], DPM1 [63]</td>
</tr>
</tbody>
</table>
## Dystrophinopathies

Dystrophinopathies include a spectrum of muscle diseases associated with the **DMD** gene, such as Duchenne and Becker muscular dystrophy [64]. The DMD is an X-linked gene, and carrier females can be asymptomatic, or may develop cardiomyopathy.

**DMD** [64]

## Other Neuromuscular Disorders

### Congenital myasthenic syndromes

**Description**

Congenital myasthenic syndromes (CMS) are heterogeneous inherited disorders of neuromuscular transmission characterized by fatigable weakness of the skeletal muscle with onset at or shortly after birth or in early childhood [87]. Severity and progression can vary. Major findings in the neonatal onset subtype include feeding difficulties, poor suck and cry, choking spells, ptosis, facial, bulbar and generalized weakness [87]. Later childhood onset subtypes show abnormal muscle fatigability, delayed motor development, ptosis, and fixed or fluctuating extracranial muscle weakness [87]. Inheritance of CMS can be either autosomal recessive or autosomal dominant.

**Typically Associated Genes**

- **ALG14** [88], **ALG2** [88], **AGRN** [89], **CHAT** [87], **CHRNA1** [87], **CHRNB1** [87], **CHRND** [87], **CHRNE** [87], **COLO** [90], **DOK7** [91], **GFPT1** [92], **LRP4** [93], **MUSK** [87], **PREPL** [94], **RAPSN** [95], **SCN4A** [96], **DPGAT1** [97], **SYT2** [98], **COL13A1** [99], **LAMB2** [100], **SNAP25** [101]

### Pompe disease

**Description**

Biallelic mutations in GAA are associated with glycogen storage disease type II (Pompe disease). Classic infantile Pompe disease is characterized by infantile onset hypotonia, muscle weakness, cardiomegaly and hypertrophic cardiomyopathy [102]. Non-classic infantile onset and late-onset forms of the disease also exist, which are also associated with slowly progressive muscle weakness [103].

**Typically Associated Genes**

- **GAA** [104]
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Gene(s)</th>
</tr>
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<tbody>
<tr>
<td>McArdle disease</td>
<td>Biallelic mutations in <em>PYGM</em> are associated with McArdle disease, or glycogen storage disease type V. This condition is characterized by muscle cramping and exercise intolerance with onset in childhood or adolescence, with progressive muscle weakness and atrophy into adulthood. Rhabdomyolysis leading to myoglobinuria can cause renal failure in some patients with McArdle disease. [OMIM#232600]</td>
<td><em>PYGM</em></td>
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<tr>
<td>Glycogen storage disease IV</td>
<td>Type 4 glycogen storage disease (GSD4) is caused by biallelic mutations in <em>GBE1</em>. GSD4 is characterized by liver disease in childhood which progresses to lethal cirrhosis. The neuromuscular presentation of GSD4 is distinguished by age of onset. These forms include a perinatal lethal type, congenital, childhood with or without cardiomyopathy, and adult with isolated myopathy or adult polyglucosan body disease.</td>
<td><em>GBE1</em> [105]</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome</td>
<td>Biallelic mutations in <em>CHST14</em> are associated with a musculocontractural form of EDS which is characterized by craniofacial dysmorphism, congenital contractures of the thumbs and fingers, clubfeet, kyphoscoliosis, hypotonia, hyperextensibility and hypermobility, and ocular involvement. Homozygous or compound heterozygous mutations in <em>FKBP14</em> are associated with Ehlers-Danlos syndrome with progressive kyphoscoliosis, myopathy and hearing loss.</td>
<td><em>CHST14</em> [106], <em>FKBP14</em> [107], <em>TNXB</em> [108]</td>
</tr>
</tbody>
</table>

**Test methods:**

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All novel and/or potentially pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. This assay also includes analysis for the recurrent c.930+189C>T deep intronic variant in the *COL6A1* gene.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

**Neuromuscular Disorders Panel (mutation analysis of 113 genes)**

- **Sample specifications:** 3 to 10 cc of blood in a purple top (EDTA) tube
- **Cost:** $2,000
- **CPT codes:** 81406, 81407
- **Turn-around time:** 8 weeks

*Note: We cannot bill insurance for the this panel*

**Congenital Muscular Dystrophy-Dystroglycanopathy Panel (mutation analysis of 14 genes)**

- **Sample specifications:** 3 to 10 cc of blood in a purple top (EDTA) tube
- **Cost:** $2,000
- **CPT codes:** 81406, 81407
- **Turn-around time:** 8 weeks

*Note: We cannot bill insurance for the this panel*

**Nemaline Myopathy Panel (mutation analysis of 10 genes)**
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks

Note: We cannot bill insurance for this panel

Bethlem Myopathy and Ullrich Muscular Dystrophy Panel (mutation analysis of 4 genes)
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks

Note: We cannot bill insurance for this panel

Centronuclear Myopathy Panel (mutation analysis of 7 genes)
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks

Note: We cannot bill insurance for this panel

Congenital Myopathy with Fiber-Type Disproportion Panel (mutation analysis of 7 genes)
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks

Note: We cannot bill insurance for this panel

Multiminicore Disease Panel (mutation analysis of RYR1 and SEPN1)
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks

Note: We cannot bill insurance for this panel

Myopathy with Tubular Aggregates Panel (mutation analysis of Orai1 and STIM1)
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks

Note: We cannot bill insurance for this panel

Emery-Dreifuss Muscular Dystrophy Panel (mutation analysis of 6 genes)
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $2,000
CPT codes: 81406
81407
Turn-around time: 8 weeks

Note: We cannot bill insurance for this panel

Results:
Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire Neuromuscular Disorders Sequencing Panel. All abnormal results are reported by telephone.


Sparks, S., et al., Congenital Muscular Dystrophy Overview, 1993.


Sparks, S., Congenital Muscular Dystrophy Overview, 1993.


