Neuromuscular Disorders Panel: Sequencing and CNV Analysis

**Test Code:** MNEU1  
**Turnaround time:** 6 weeks  
**CPT Codes:** 81404 x1, 81405 x1, 81406 x1, 81407 x1, 81408 x1, 81400 x1, 81401 x1

### Condition Description

The neuromuscular disorders (NMD) are a group of conditions that affect the peripheral nervous system and muscles. Primarily, they affect the ability to perform voluntary movements. They range in onset from before a child is born to much later in life with the majority beginning during infancy, childhood, or the teenage years. With many of the neuromuscular disorders overlapping in their clinical and/or pathological phenotypes, molecular testing can be necessary to pinpoint the precise disorder a patient has.

The Neuromuscular Disorders Panel includes testing for nemaline myopathy, limb girdle muscular dystrophy, Emery-Dreifuss muscular dystrophy, congenital muscular dystrophy, Zellweger syndrome spectrum, and cardiomyopathies. Individual disorders included on this panel are myoadenylate deaminase deficiency, erythrocyte AMP deaminase deficiency, myofibrillar myopathy, Duchenne/Becker muscular dystrophy, congenital disorder of glycosylation type 1a, malignant hyperthermia susceptibility, myoclonus dystonia, Marinesco-Sjogren syndrome, and distal arthrogryposis.

Note: This test does not detect the retrotransposon insertion in the 3' UTR of the FKTN gene common in some Asian populations. For patients with suspected Fukuyama congenital muscular dystrophy, testing for the FKTN insertion is recommended. Analysis for the FKTN insertion is available as a separate assay.

**Reference:**

### Genes

ACTA1, AMPD1, ANOS1, CAPN3, CAV3, COL6A1, COL6A2, COL6A3, CRPPA, DES, DMD, DYSF, EMD, FKRP, FKTN, GAA, GNE, ITGA7, LAMA2, LARGE1, LMNA, MYOT, NEB, PLEC, PMM2, POMT1, POMT2, PYGM, RYR1, RYR2, SELENON, SGCA, SGCB, SGCD, SGCE, SGCG, SILL1, TCAP, TNNT2, TNNT1, TPM2, TPM3, TRIM32, TTN, VCP

### Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of neuromuscular disorders.

### Methodology

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Copy Number Analysis:** Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

### Detection

**Next Generation Sequencing:** Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical sensitivity for sequence variant detection is ~99%.

**Copy Number Analysis:** The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

### Specimen Requirements

**Submit only 1 of the following specimen types**

**Type:** Saliva

**Specimen Requirements:**
Oragene™ Saliva Collection Kit
Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: DNA, Isolated

Specimen Requirements:
Microtainer
8µg
Isolation using the Perkin Elmer™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Whole Blood (EDTA)

Specimen Requirements:
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old): 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Related Tests

- Single-gene testing is available for most genes on this panel.
- Limb-Girdle Muscular Dystrophy: Sequencing Panel.
- Congenital Muscular Dystrophy: Sequencing Panel.
- Bethlem Myopathy/Ullrich Congenital Muscular Dystrophy Panel.
- Expanded Neuromuscular: Sequencing Panel.
- Neuromuscular Disorders: Deletion/Duplication Panel.