Spinal Muscular Atrophy (SMA) is the second most common lethal, autosomal recessive disorder in Caucasians, with an incidence of approximately 1/10,000 and a carrier frequency of 1/50. SMA is characterized by anterior horn cell degeneration which causes a symmetrical muscle weakness and wasting. SMN1 is deleted in about 95% of individuals with SMA. This carrier assay tests for the common SMN1 deletion only; other pathogenic copy number variants will not be detected.

Approximately 5-8% of carrier individuals will have a normal SMN1 copy number of two, but both copies will be on the same chromosome (in cis) with a deletion on the second chromosome. This assay will not detect these carrier individuals. This assay will not report SMN2 copy number.

Although a positive test result should not affect the health of the individual, she could be at a 25% risk for passing that condition on to her children depending on the carrier status of the partner. In addition to the specific pathogenic variants identified by the panel, Emory Genetics Laboratory also offers single-gene, full gene sequencing for genes on the panel, which can be utilized to screen partners of positive carriers. Knowing about these risks ahead of time can help couples make decisions about testing options prior to and during pregnancy, and can help healthcare providers be more readily prepared to offer appropriate follow-up care at delivery.

### Genes

- ABCC8, ASPA, BCKDHB, BLM, CFTR, CLRN1, DLD, ELP1, FANCC, FKTN, FMR1, G6PC, GBA, HEXA, MCOLN1, NEB, PCDH15, SMN1, SMPD1, TMEM216

### Indications

Appropriate for:

- Carrier testing in individuals of Ashkenazi Jewish descent.

### 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. Only known pathogenic variants will be reported.

**Fragile X Syndrome Repeat Analysis:** Both normal CGG repeat tracts and expanded CGG repeat tracts are detected by PCR amplification, using a CGG repeat-specific probe, and capillary electrophoresis. Expanded CGG repeat tracts will be reflexed to a gene specific PCR and sized by agarose electrophoresis followed by in-solution hybridization to detect full mutations. The assay also detects premutation, at-risk, and normal CGG repeats.
gel electrophoresis.

**Spinal Muscular Atrophy (SMA) Testing:** SMN1 gene deletions were quantified by multiplex ligation polymerase chain reaction amplification (MLPA) of exons 7 and 8. Gene dosage ratios of SMN1 are calculated relative to the average of 16 reference loci and are expressed as gene dosage, and/or copy number. Diploid gene dose or 2 copies of SMN1 indicates normal (not affected) status, 1x gene dosage or 1 copy of the SMN1 gene most likely indicates carrier status and deletions (less than 0.1x) of SMN1 or 0 copies of the SMN1 gene designates affected status. This carrier assay tests for the common SMN1 deletion only; other pathogenic variants will not be detected. SMN2 copy number is not assessed.

### Detection

**Next Generation Sequencing:** Next Generation Sequencing: Clinical Sensitivity: See results report. Pathogenic variants in regions other than the targeted area, including the promoter region, some mutations in the introns and other regulatory element mutations, cannot be detected by this analysis. Large deletions/duplications will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical Sensitivity: ~99%.

**For Fragile X Syndrome Repeat Analysis:** All cases of fragile X syndrome caused by CGG expansion will be detected by this assay. Rare cases of fragile X syndrome caused by pathogenic variants in the FMR1 gene will not be detected by this assay.

**For Spinal Muscular Atrophy (SMA) Testing:** Deletions of the SMN1 gene are found in approximately 95% of individuals with SMA. This carrier assay tests for the common SMN1 deletion only; other pathogenic variants will not be detected. Approximately 5-8% of carrier individuals will have a normal SMN1 copy number of two, but both copies will be on the same chromosome (in cis) with a deletion on the second chromosome. This assay will not detect these carrier individuals. SMN2 copy number is not assessed.

### Reference Range

**For Fragile X Testing:**
- Normal: Approximately 5-44 CGG repeats.
- Intermediate: Approximately 45-54 unmethylated CGG repeats.
- Premutation: Approximately 55-200 CGG repeats and methylation of expanded allele.
- Affected: Over 200 CGG repeats and methylation of expanded allele.

### Specimen Requirements

Submit only 1 of the following specimen types

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection Kit.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml.

Specimen Collection and Shipping: Ship sample at room temperature with overnight delivery.

**Type: Isolated DNA**

Specimen Requirements:

In microtainer: 60 ug

Isolation using the Qiagen™ Puregene kit for DNA extraction is recommended.

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

### Related Tests

- Ashkenazi Jewish Carrier Screen: Targeted Mutation Panel
- Pan-Ethnic Carrier Screen: Gene Sequencing Panel
- ACOG/ACMG Carrier Screen: Gene Sequencing Panel