**Ashkenazi Jewish Carrier Screen: Targeted Mutation Panel**

**Test Code:** MM510  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81209 x1, 81220 x1, 81243 x1, 81251 x1, 81330 x1, 81332 x1, 81400 x1, 81401 x1, 81205 x1

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### Condition Description

Individuals of Ashkenazi Jewish descent are at a higher risk than the general population to be carriers of certain genetic diseases. This carrier screening panel tests for 20 of these diseases. The panel meets the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) Ashkenazi Jewish ancestry carrier screening recommendations, and also includes additional diseases that occur more frequently in this population.

For more information on individual diseases, please visit the [Emory Jewish Genetic Disease Program](http://www.emory.edu/JGDP) website.

Click [here](http://www.emory.edu/JGDP) for a complete list of mutations.

Note that the quoted detection rates and residual carrier risks are directly applicable only to persons of Ashkenazi Jewish descent. The carrier detection rate in persons from other ethnic backgrounds is likely to be significantly lower.

- **Condition**  
- **Gene**  
- **Mutations**  
- **Detection Rate**  
- **Carrier Frequency**  
- **Residual Carrier Risk if Negative**

<table>
<thead>
<tr>
<th>Condition</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>ABCC8-Related Familial Hyperinsulinism</strong></td>
<td><strong>ABCC8</strong></td>
<td>F1388del, 3989-9G&gt;A, V187D</td>
<td>88%</td>
<td>1 in 66</td>
<td>1 in 542</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2281del6ins7*, 2407insT, Q645X, Q700X, R899X</td>
<td>97%</td>
<td>1 in 100</td>
<td>1 in 3301</td>
</tr>
<tr>
<td><strong>Bloom Syndrome</strong></td>
<td><strong>BLM</strong></td>
<td>433-2A&gt;G, Y231X*, A305E, E288A*</td>
<td>99%</td>
<td>1 in 40</td>
<td>1 in 3901</td>
</tr>
<tr>
<td><strong>Canavan Disease</strong></td>
<td><strong>ASPA</strong></td>
<td>142 mutation panel including 23 ACMG recommended mutations (see below)</td>
<td>97%</td>
<td>1 in 25</td>
<td>1 in 801</td>
</tr>
<tr>
<td><strong>Cystic Fibrosis</strong></td>
<td><strong>CFTR</strong></td>
<td>844G*, del55bp, IVS2-1G&gt;A*, D409H, D409V, L444P, N370S*, R463C, R463H, R496H, V394L</td>
<td>95%</td>
<td>1 in 14</td>
<td>1 in 261</td>
</tr>
<tr>
<td><strong>Gaucher Disease Type 1</strong></td>
<td><strong>GBA</strong></td>
<td>79delC, 378dupTA, 979del3, 648G&gt;T, E242X, R83C, R83H, G188R, G270V, Q347X</td>
<td>99%</td>
<td>1 in 71</td>
<td>1 in 7001</td>
</tr>
<tr>
<td><strong>Glycogen Storage Disease Type 1a</strong></td>
<td><strong>G6PC</strong></td>
<td>79delC, 378dupTA, 979del3, 648G&gt;T, E242X, R83C, R83H, G188R, G270V, Q347X</td>
<td>99%</td>
<td>1 in 92</td>
<td>1 in 9101</td>
</tr>
<tr>
<td><strong>Joubert Syndrome Type 2</strong></td>
<td><strong>TMEM216</strong></td>
<td>E372X, G278S, R183P</td>
<td>99% for MSUD type 1B; 1 in 81</td>
<td>1 in 181</td>
<td>1 in 667</td>
</tr>
<tr>
<td><strong>MSUD Type 3</strong></td>
<td><strong>DLD</strong></td>
<td>105insA (Y35X), G229C</td>
<td>95%</td>
<td>1 in 96</td>
<td>1 in 1901</td>
</tr>
<tr>
<td><strong>Mucolipidosis Type IV</strong></td>
<td><strong>MCOLN1</strong></td>
<td>Exon1 - Exon7del (Del6,4kb)<em>, IVS3-2A&gt;G</em></td>
<td>95%</td>
<td>1 in 125</td>
<td>1 in 2481</td>
</tr>
<tr>
<td><strong>Nemaline Myopathy</strong></td>
<td><strong>NEB</strong></td>
<td>R247A_DS2512del</td>
<td>99%</td>
<td>1 in 108</td>
<td>1 in 10701</td>
</tr>
<tr>
<td><strong>Niemann-Pick Type A</strong></td>
<td><strong>SMPD1</strong></td>
<td>R610del, H423Y, L302P*, R469L, T324I</td>
<td>97%</td>
<td>1 in 90</td>
<td>1 in 2967</td>
</tr>
<tr>
<td><strong>Tay-Sachs Disease</strong></td>
<td><strong>HEXA</strong></td>
<td>1278insTATC*, del17.5kb, 1421+1G&gt;C*, IVS7-1G&gt;A, IVS9-1G&gt;A, E462V, G250D, G269S*, R170W, R178H, R247W, R249W</td>
<td>98% (including enzyme analysis)</td>
<td>1 in 25</td>
<td>1 in 1201</td>
</tr>
<tr>
<td><strong>Usher Syndrome Type IF</strong></td>
<td><strong>PCDH15</strong></td>
<td>R245X</td>
<td>75%</td>
<td>1 in 141</td>
<td>1 in 561</td>
</tr>
<tr>
<td><strong>Usher Syndrome Type III</strong></td>
<td><strong>CLRN1</strong></td>
<td>459 del3, L150P, M120K, N48K, Y176X</td>
<td>98%</td>
<td>1 in 107</td>
<td>1 in 5301</td>
</tr>
<tr>
<td><strong>Walker-Warburg Syndrome</strong></td>
<td><strong>FKTN</strong></td>
<td>1167dupA, R47X, 647+2084G&gt;T</td>
<td>99%</td>
<td>1 in 112</td>
<td>1 in 10,000</td>
</tr>
</tbody>
</table>

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Fragile X Syndrome

Fragile X syndrome is characterized by moderate intellectual disability in affected males. Affected females may show mild intellectual disability. It has a prevalence of 1/4000 to 1/6000 in the general population, and is a leading genetic cause of intellectual disability. Fragile X syndrome is associated with a triplet (CGG) repeat expansion in the promoter of the FMR1 gene on the X chromosome. CGG expansion leads to methylation and subsequent inactivation of the FMR1 gene. Normal alleles have ~5-44 repeats. Intermediate alleles have ~45-54 repeats and may expand in subsequent generations to premutation alleles. Alleles with ~55-200 repeats are called premutation alleles and may expand in subsequent generations to full mutations, especially when passed from mother to child. Alleles over ~200 repeats are full mutations and will cause fragile X syndrome in males.

Please note this panel will be performed and reported on both male and female specimens. Because of the nature of X-linked inheritance, this test, if positive, may be diagnostic for male patients in rare cases. If you do not wish to have X-linked conditions assessed in male patients, please contact the laboratory.

Spinal Muscular Atrophy

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 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, EGL Genetics 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

| ABCG8, 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 the regions encompassing the targeted pathogenic variants is performed on the patient’s genomic DNA. 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 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:** 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 other pathogenic variants in the FMR1 gene will not be detected by this assay.
**For Spinal Muscular Atrophy (SMA) Testing:** Deletions of the \textit{SMN1} gene are found in approximately 95\% of individuals with SMA. This carrier assay tests for the common \textit{SMN1} deletion only; other pathogenic variants will not be detected. Approximately 5-8\% of carrier individuals will have a normal \textit{SMN1} copy number of two, but both copies will be on the same chromosome (\textit{in cis}) with a deletion on the second chromosome. This assay will not detect these carrier individuals. \textit{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: 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.

**Type: DNA, Isolated**

**Specimen Requirements:**
- Microtainer
  - 20\µg
  - Isolation using the Perkin Elmer™Chemagen™ 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.

**Related Tests**

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