Carrier screening for recessive conditions

This component of the Pan-Ethnic Carrier Screen tests 138 genes that cause autosomal recessive conditions. It is the most extensive carrier screen to date and includes conditions of mobility, developmental delay, visual impairment, hearing loss, intellectual disability, skin irregularities, joint and bone disorders, abnormalities of the nervous system, and numerous metabolic syndromes. None of these conditions has a cure, but some can be well managed with diet or medication (e.g., PKU or biotinidase deficiency). Many of these conditions, however, can result in a shortened lifespan or require continued medical care (e.g., Tay-Sachs disease or cystic fibrosis).

Carrier screening for X-linked conditions, including fragile X syndrome repeat analysis

This component of the test screens 10 genes that cause X-linked recessive conditions. This testing includes repeat analysis for fragile X syndrome, the most common genetic form of intellectual disability in males. Females who are carriers for one of these conditions are at risk to pass the disease on to their sons.

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.

Carrier screening for spinal muscular atrophy (SMA)

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. While the specific risks will vary, the Pan-Ethnic Carrier Screen is appropriate for individuals of all ethnicities.

Genes

<table>
<thead>
<tr>
<th>Genes</th>
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<tbody>
<tr>
<td>ABC28, ACADM, ACADS, ACADVL, ACAT1, AGA, AGRT, AIRE, ALDH3A2, ALDOB, ALPL, ARSA, ARSB, ASL, ASPA, ASS1, ATM, ATRP7B, BBS1, BBS10, BCKDHA, BCKDHB, BCS1L, ELM, BTD, CAPN3, CBS, CCN6, CFTR, CHM, CLN3, CLN5, CLN8, CLRN1, CNGB3, CPT1A, CPT2, CTNS, CTSC, CTSK, CYPB1, CYPC1B1, DMT, DMD, DPDY, EDAR, ELPL1, F11, F9, FAH, FANCC, FH, FHTN, FMR1, G6PC, G6PD, GAA, GALC, GALNS, GALT, GBA, GCH2, GHRPR, GJB2, GJB6, GLA, GLB1, GNE, GNPTAB, GP1BB, GP9, GRHPR, GUSB, HADHA, HBA1, HBA2, HBB, HEXA, HEXT, HFE, HMX1, HSDBP4, IDS, IDUA, IVD, LAMA1, LAMB3, LAMC2, LIPA, MAN2B1, MCOLN1, MECP2, MEFV, MLC1, MMAA, MMEB, MMACHC, MMUT, MPI, MGLUL, NBN, NBR, NLRP7, NPC1, NPC2, NPHS1, NPHS2, OPA3, OTC, PAH, PANK2, PCDH15, PEX1, PEX7, PHGDH, PMM2, PMOMNT1, PPT1, PRO1, PYGM, RMRP, RS1, SAC3, SERPINA1, SGCA, SGCG, SGCG, SLC12A6, SLC17A5, SLC19A2, SLC22A5, SLC26A2, SLC26A4, SLC37A4, SMN1, SMND1, TH, TMEM216, TTP1, TTC37, TTPA, TYR, VPS13B, WRN</td>
</tr>
</tbody>
</table>

Indications

This test is indicated for:

- Individuals or couples seeking to assess reproductive risk for a variety of conditions.
- Individuals or couples of high-risk ethnic groups or backgrounds.

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.
**RMRP** belongs to a family of genes called small miscellaneous non-coding RNAs. Full sequencing is not performed on this gene; rather only the single 70A→G mutation in this gene is analyzed.

**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:** The 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.

**Deletion/Duplication Analysis:** DNA isolated from peripheral blood is hybridized to a gene-targeted CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes that cover the entire genomic region. Please note that only the following genes are included in the deletion/duplication analysis component of this panel: CFTR, DMD, and MECP2.

**Alpha-thalassemia Analysis:** Copy number changes in the HBA1 and HBA2 genes are detected using multiplex ligation polymerase chain reaction amplification (MLPA). This assay identifies the hemoglobin Constant Spring (HbCS) mutation, as well as common deletions associated with alpha-thalassemia, including the 3.7, 4.2, Southeast Asian, Filipino, and Thailand deletions.

**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.

**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 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.

**Deletion/Duplication Analysis:** Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype. Only the following genes are included in the deletion/duplication analysis: CFTR, DMD, and MECP2.

**Alpha-thalassemia Analysis:** This assay will detect the pathogenic variants specified above (Methodology Section), accounting for over 90% of alpha-thalassemia cases. The presence of less common deletions may also be detected by MLPA.

**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:** DNA, Isolated

**Specimen Requirements:**
- Microtainer
- 20µg
  - 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.

**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 24 hours of collection. Do not refrigerate or freeze.

Related Tests

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

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