Pan-Ethnic Carrier Screen: Targeted Mutation Panel

Test Code: MM480
Turnaround time: 2 weeks

CPT Codes: 81200 x1, 81205 x1, 81209 x1, 81220 x1, 81616 x1, 81243 x1, 81251 x1, 81304 x1, 81332 x1, 81400 x1, 81401 x1, 81404 x1

Condition Description

Test components:

- Carrier screening for recessive conditions
- Carrier screening for X-linked conditions

Click here for a complete list of mutations.

Carrier screening for recessive conditions

This component of the Pan-Ethnic Carrier Screen tests for 690 pathogenic variants in 135 genes, as well as full gene deletion and duplication analysis for 3 genes (CFTR, HBA1, and HBA2) causing 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 bionidiase 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 for 30 pathogenic variants in 8 genes causing X-linked recessive conditions, as well as full gene deletion/duplication analysis of 2 additional genes (DMD and MECP2). 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.

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 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

ACCC8, ACADM, ACADS, ACADVL, ACAT1, AGA, AGT, AIRE, ALDH3A2, ALDOB, ALPL, ARSA, ASL, ASPA, ASS1, AT1M, ATP7B, BBS1, BBS10, BCKDHA, BCKDHB, BCSD1, BLM, BTD, CAPN3, CBS, CCN6, CFTR, CHM, CLN3, CLN5, CLN6, CTRN1, CNGB3, CPT1A, CPT2, CTNS, CTSC, CTSH, CYP1B1, CYP21A2, DBT, DHDPR, DLD, DMD, DPYD, DQAR, ELPA1, E1F1, F8, FAH, FANCC, FH, FKTN, FMRI, G6PC, G6PD, GAA, GALC, GALS, GALT, GBA, GCODH, GHRPR, GJB2, GJB6, GLA, GLB1, GNE, GNPTAB, GP1BB, GP9, GRHPR, GUSB, HADHA, HBA1, HB2, HBB, HEXA, HEXB, HFE, HMX1, HSD17B4, IDS, IDUA, IVD, LAMA3, LAMB3, LAMC2, LIPH, MAN2B1, MCOLN1, MECP2, MEFV, MLC1, MMEA, MMACHC, MMATU, MPI, NAGLU, NBN, NCS, NLRP7, NPC1, NPC2, NPHS1, NPHS2, OPA3, OTC, PAH, PANK2, PCDH11S, PEK1, PEX7, PKH1, PPM1M2, POMGNT1, PPT1, PRO1P1, PYGM, RS1, SAC, SERP1A1, SGCA, SGCB, SGCG, SGSH, SLCL2A6, SLCL7A5, SLCL9A2, SLCC2A5, SLCC6A5, SLCC6A4, SLCC7A4, SMN1, SMPL1, TH, TMEM216, TPP1, TTC37, TPPA, TTYR, VPS13B, WBN

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 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

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the common \textit{SMN1} deletion only; other pathogenic variants will not be detected. \textit{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: \textit{CFTR}, \textit{DMD}, and \textit{MECP2}.

**Alpha-thalassemia Analysis:** Copy number changes in the \textit{HBA1} and \textit{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.

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 \textit{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.

**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: \textit{CFTR}, \textit{DMD}, and \textit{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

<table>
<thead>
<tr>
<th>Specimen Requirements:</th>
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<tr>
<td>Microtainer</td>
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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:**

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<tr>
<th>EDTA (Purple Top)</th>
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<tr>
<td>Infants and Young Children (2 years of age to 10 years old): 3-5 ml</td>
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<tr>
<td>Older Children &amp; Adults: 5-10 ml</td>
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<tr>
<td>Autopsy: 2-3 ml unclotted cord or cardiac blood</td>
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**Specimen Collection and Shipping:**
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

**Related Tests**

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