1274 Genetic Carrier Screening Panel (3 genes) includes:

- Cystic Fibrosis Core Test (23 major CFTR variants approved by ACOG/ACMG)
- Fragile X Syndrome
- Spinal Muscular Atrophy

1247 Genetic Carrier Screening Ashkenazi Panel (43 genes) includes:

- Abetalipoproteinemia (MTTP)
- Alport Syndrome (COL4A3)
- Arthrogryposis, Mental Retardation, and Seizures
- Bardet-Biedl Syndrome Bloom Syndrome
- Canavan Disease
- Carnitine Palmitoyltransferase II Deficiency
- Congenital Amegakaryocytic Thrombocytopenia
- Congenital Disorder of Glycosylation Type 1a
- Cystic Fibrosis Comprehensive Test (191 variants)
- Dyskeratosis Congenita
- Ehlers-Danlos Syndrome Type VIIC
- Familial Dysautonomia
- Familial Hyperinsulinism
- Fanconi Anemia Type C
- Fragile X Syndrome
- Galactosemia
- Gaucher Disease
- Glycogen Storage Disease 1a
- Joubert Syndrome
- Maple Syrup Urine Disease Types 1a, 1b, 3
- Mucolipidosis Type IV
- Multiple Sulfatase Deficiency
- Nemaline Myopathy
- Niemann-Pick Disease
- Phosphoglycerate Dehydrogenase Deficiency
- Polycystic Kidney Disease, Autosomal Recessive
- Retinitis Pigmentosa 59
- Smith-Lemli-Opitz Syndrome
- Spinal Muscular Atrophy
- Tay-Sachs Disease
- Tyrosinemia Type 1
- Usher Syndrome Type 1F and III
- Walker-Warburg Syndrome
- Wilson Disease
- Zellweger Spectrum Disorder

The classification and interpretation of all genetic variants identified as a result of this genetic testing is based on the current scientific information available. As new scientific information becomes available, in some circumstances, the classification and interpretation of the genetic variants may change. All test results should be interpreted by a physician or genetic counselor in the context of the personal/family history, and clinical and laboratory data. A "Positive" test result indicates the person is at higher risk for having a child with a genetic condition. Partner testing should be considered. Genetic counseling is recommended to review results, discuss additional testing possibilities, and evaluate any next steps.

The patient was NEGATIVE for the variants tested for all other diseases. These results reduce, but do not eliminate, the chance to be a carrier. See carrier screening residual risk table for disease-specific details.

Methods and Variant Classification:
Genomic DNA is extracted from blood or mouth wash sample. High-throughput next generation sequencing is performed to examine for the over 1,300 DNA variants which are associated with 41 diseases. Some mutations are more severe than others. These variant regions are sequenced to high coverage and the sequences are compared to standards and references of normal variation. All reported variants are confirmed by the "gold standard" Sanger sequencing. In addition, some of the variants on the panel may be partially subjected to Sanger sequencing due to inadequate sequence coverage by next generation sequencing.

The MLD variant classification system is based on the 5-tier system recommendations for the interpretation of sequence variants proposed by the American College of Medical Genetics and Genomics (ACMG), and complex with the standards and guidelines for the interpretation of sequence variants by ACMG and the Association for Molecular Pathology (AMP) (Reference 1). To classify each variant, MLD assigns weight to each piece of available evidence, including literature reviews, reputable database reports, population frequencies, and computational In Silico analysis using PROVEAN, SIFT and MutationTaster and prediction.

Any detected variants that are a recognized cause of the disease (Pathogenic) will be reported. In addition, variants that have not previously been established as a recognized cause of disease may be identified. In these cases, variants classified as "likely" pathogenic are reported too. Benign variants, likely benign variants and variants of uncertain significance, and variants not directly associated with the intended disease phenotype are not reported.

MLD variant results are reported using numbering and nomenclature recommended by the Human Genome Variation Society (HGVS) http://www.hgvs.org). All results are reported in reference to Human Genome 19, Human Build 37.

Residual Risk:
Residual risk is the possibility of being a carrier in the case of a negative test result for any genetic disease tested. A negative result for any of the diseases tested in the MLD carrier screening panel significantly decreases a person’s risk of being a carrier for this genetic condition. However, it is still possible to be a carrier for a disease.

In an unknown number of cases, nearby genetic variants may interfere with mutation detection. Other possible sources of diagnostic error include sample mix-up, trace contamination, bone marrow transplantation, blood transfusions and technical errors. If more than one variant is detected in a gene, additional studies may be necessary to determine if those variants exist on the same chromosome or on different chromosomes.

Test Limitations:
The MLD carrier screen panel analyses over 1,300 known targeted variant genetic diseases and selected for relatively high frequency in the general population and for each ethnic group. Interpretations and risk calculations are based on understanding of the molecular genetics of the conditions tested.

This test does not rule out the presence of disease-causing variants in other genes that will not detect germline mosaicism. Because of this, the MLD test is risk-rule out carrier for additional variants not screened for in this test and are dependent on ethnicities may experience better carrier detection with other testing methods.

In an unknown number of cases, nearby genetic variants may interfere with mutation detection. Other diagnostic errors include sample mix-up, trace contamination, bone marrow transplantation, blood transfusions and technical errors. If more than one variant is detected in a gene, additional studies may be necessary to determine if those variants exist on the same chromosome or on different chromosomes.

Disclaimer:
This test was developed and its performance characteristics have been determined in analytical performance of the test. It has not been reviewed by the US Food and Drug Administration.

References/Footnotes:


definitions:
- **Positive**: Risk for having a child with a genetic condition
- **Negative**: Risk for having a child with a genetic condition is significantly reduced
- **Genetic Carrier Screening Society-Guided Panel (9 genes)**
- **Interpretation Summary**
  - **Variant Classification**: Pathogenic, Likely Pathogenic, Benign, Likely Benign, Variants of Uncertain Significance
  - **Variant Reporting**: MLD assigns weight to each piece of available evidence, including literature reviews, reputable database reports, population frequencies, and computational In Silico analysis using PROVEAN, SIFT and MutationTaster and prediction.

<table>
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<tr>
<th>Gene</th>
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<th>Location</th>
<th>Disease</th>
<th>Parental Origin</th>
<th>Classification</th>
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<td>Bloom Syndrome</td>
<td>Autosomal</td>
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</table>

### Comprehensive Interpretation:
**Test Interpretation:**
Sequencing of the known disease-associated mutations of 41 rare genetic disease-related genes was completed. The patient was POSITIVE for the variant c.2207_2212delATCTGAinsTAG TTC (p.Tyr73Leufs) in the BLM gene. This change has been associated with Bloom Syndrome and is considered to be the cause of the disorder. This variant was identified by Next Generation Sequencing (NGS) and classified using the MLD variant classification system (see below for detail). This variant is predicted to cause a frameshift, which alters the protein’s amino acid sequence beginning at position 736 and leads to a premature termination codon 5 amino acids downstream. This alteration is then predicted to lead to a truncated or absent protein.