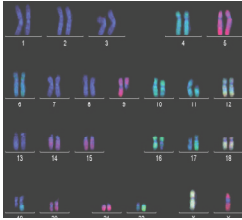


MEDICAL DIAGNOSTIC LABORATORIES, L.L.C.

Ashkenazi Jewish Genetic Carrier Screening Assays



Recent advances in genetic research have identified a series of disorders that are most prevalent in the Ashkenazi Jewish population, though not exclusively. These disorders are inherited in an autosomal recessive manner which translates into a 25% chance of transmission to offspring when both parents are carriers. Fortunately, the risk of transmission is significantly decreased when one parent is proven not to harbor these critical mutations.

In 2004, the American College of Obstetricians and Gynecologists (ACOG) recommended that all couples of Ashkenazi Jewish ancestry be offered carrier screening for Tay-Sachs Disease, Cystic Fibrosis, Canavan Disease and Familial Dysautonomia. Furthermore, such potential parents are to be made aware of the availability of tests for Mucopolidosis Type IV, Niemann-Pick Type A Disease, Fanconi Anemia Type C, Bloom Syndrome and Gaucher Disease before conception. MDL is pleased to announce the availability of testing for nine commonly inherited disorders on the **OneSwab**[®] platform. MDL's Test 1213 Ashkenazi Jewish Carrier Screening Panel by Bio-Plex Analysis consists of the four carrier screening tests recommended by ACOG for all couples of Ashkenazi Jewish ancestry. Test 1214 Ashkenazi Jewish Carrier Screening Expanded Panel by Bio-Plex Analysis includes all nine of the tests mentioned in the ACOG recommendation. All nine tests are available individually as well.

Test 1207: Bloom Syndrome by Bio-Plex analysis

An extremely rare genetic disorder resulting from various mutations within the Bloom (BLM) gene, a DNA helicase. These mutations, though not lethal, increase the rate of chromosomal instability and the risk of early onset cancers; this predisposition often results in premature death of affected individuals in their twenties or thirties. Chronic lung problems, diabetes mellitus, male sterility and immune deficiencies are also associated with this syndrome. Although there is no direct form of treatment for Bloom Syndrome, management can be achieved through preventive therapies.

Ashkenazi Carrier Rate: 1:104

Test 1209: Canavan Disease by Bio-Plex analysis

A genetic disorder that occurs with greatest frequency among Jewish individuals of Ashkenazi descent. The disease, a result of various mutations within the aspartoacylase (ASPA) gene, leads to a host of neurological disorders and motor skill deficiencies within affected individuals. The aspartoacylase enzyme is critical to the maintenance and growth of myelin sheaths within the brain. Symptoms begin to emerge within the first nine months of life and are typified by increased head circumference and the lack of head control and visual responsiveness. There is no standard measure of treatment, but a lack of any medical intervention usually results in death by the age of four.

Ashkenazi Carrier Rate: 1:40

Test 1201: Cystic Fibrosis Gene Carrier Screening by Bio-Plex Analysis

Cystic Fibrosis (CF) is an autosomal recessive inheritable disease that afflicts approximately 30,000 people within the United States and 70,000 worldwide, with 1,000 new cases diagnosed each year. Due to its recessive inheritable pattern, people may be carriers of the disease, having inherited a defective gene but not exhibiting symptoms. It is estimated that an additional ten million, or one in every thirty-one Americans, are carriers. Carrier status occurs more frequently within Ashkenazi Jewish and Caucasians of European descent populations, each of which has a one in twenty-nine carrier risk rate. The defective gene responsible for CF was identified in 1989 as the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene. The CFTR protein serves as a chloride channel within epithelial cells; disruption of its function induces an electrolyte imbalance that results in excess sodium chloride levels in sweat, a hallmark and diagnostic indicator of disease, and is believed to cause the thickening of fluids in the lungs and digestive tract. CF is a disease which affects multiple systems and organs in the body including the lungs, pancreas, intestines, and liver. The severity of symptoms associated with CF varies from person-to-person and may include very salty tasting skin, persistent coughing, frequent lung infections, wheezing, shortness of breath, poor growth and weight gain despite adequate appetite and diet, difficulty with bowel movements or frequent greasy, bulky stools. Although some individuals with a mild presentation of CF may not be diagnosed until adulthood, most CF patients will be diagnosed by 6 months of age. In general, recent medical advances have allowed the extension of the median age of survival from just a few years in the 1950's to the current rate of almost 37 years.

Ashkenazi Carrier Rate: 1:29

Test 1212: Mucopolidosis Type IV by Bio-Plex analysis

A lysosomal storage disorder resulting from mutations within the cation channel TRPML1 (Mucopolin-1), which primarily localizes to endosomes. Mutations within the MCOLN1 gene, which encodes the TRPML1 channel protein, block normal endocytic transport and prevent the formation of lysosomes. Through an as-of-yet unknown mechanism, these mutations lead to severe neurologic and ophthalmologic abnormalities. Affected children display symptoms within the first two years of life and are expected to survive into adulthood but their physical and mental development are typically stunted, advancing only to the level of a one to two year old. Treatment is limited to supportive care.

Ashkenazi Carrier Rate: 1:100

Test 1210: Familial Dysautonomia by Bio-Plex analysis

A neurological disorder primarily affecting the autonomic nervous system and, to a lesser extent, the sensory system. Also known as Riley-Day syndrome, neurological abnormalities arise due to mutations within the gene that encodes the IκB kinase complex associated protein (IKBKAP). This protein is critical to the transcriptional process and its defect decreases the number of non-myelinated neurons and also the diameter

of those neurons that are myelinated. Over the course of the individual's lifetime, these neuropathies accumulate to affect multiple organs and systems, often dramatically shortening the affected individual's lifespan. Familial Dysautonomia is rare within the general population but has a 1 in 3,700 incidence rate within the Ashkenazi Jewish population.

Ashkenazi Carrier Rate: 1:30

Test 1205: Fanconi Anemia Type C by Bio-Plex analysis

A rare, inheritable blood disorder in which the individual's bone marrow inefficiently produces the three main components of blood: platelets, red blood cells and white blood cells. Multiple organs and systems are affected within these individuals. Affected individuals are also at higher risk of genetic defects and early-onset cancers, about 10% of such individuals develop Acute Myelogenous Leukemias (AML). The major cause of death is bone marrow failure that is typified by thrombocytopenia and neutropenia that transcend into fatal pancytopenia and aplastic anemia. Medical advances have extended the life span expectancy of Fanconi Anemia patients from 20 to 30 years of age. The carrier frequency is estimated to be between 1 in 100 to 1 in 600 total births.

Ashkenazi Carrier Rate: 1:80

Test 1211: Gaucher Disease by Bio-Plex analysis

The most common lipid storage disease resulting from a deficiency in the glucocerebrosidase enzyme. The inability to breakdown the fatty substance glucocerebroside, or glucosylceramide, allows for its accumulation within many organs and joints, disrupting normal function. There are three forms of the disease, types 1 through 3. Type 1, the most common form, is limited to liver and spleen enlargement, anemia and fatigue with no neurological involvement. Type 3 has a similar symptomology but neurological defects arise over time in the form of seizures. Type 2 is typified by extensive and progressive neurological damage that often leads to death by the age of 2. Enzyme replacement therapy is efficacious for Type 1 and Type 3 forms of the disease that occur in the absence of neurological impairment. When neurological effects are observed, bone marrow transplantation is the only therapeutic option.

Ashkenazi Carrier Rate: 1:15

Test 1206: Niemann-Pick Disease Type A by Bio-Plex analysis

A lysosomal storage disease that results in a neurologic disorder resulting from the abnormal and toxic accumulation of the cholesterol, sphingomyelin, within cells. The disease can occur as one of four types, A, B, C or D, dependent upon the inheritable mutation. Types A and B occur due to a deficiency of the enzyme acid sphingomyelinase which is necessary for the removal of sphingomyelin, a fat found in all cell types. Type C occurs as a result of the inability to process cholesterol and other lipids leading to their toxic build-up, while Type D occurs due to an inability to move cholesterol among brain cells. Types A, C and D adversely affect the brain and result in a progressive loss of motor and sensory function.

Ashkenazi Carrier Rate: 1:80

Test 1208: Tay-Sachs Disease by Bio-Plex analysis

A fatal lipid storage disease resulting from the accumulation of toxic levels of the ganglioside lipid within the brain. This accumulation occurs due to the presence of mutations either within the ganglioside protein itself, resulting in its misfolding, or within the critical lysosomal enzyme beta-hexosaminidase A required for its degradation. Development appears normal

initially, but mental and physical deterioration occur quickly within the first few months of life as the fat accumulates within nerves; deafness, blindness and an inability to swallow then ensue. There is no effective treatment and death by the age of 4 years is generally a certainty.

Ashkenazi Carrier Rate: 1:28

Testing Methodology:

While most diagnostic laboratories require several milliliters of blood, our **OneSwab**[®] technology provides a minimally invasive collection method that provides sufficient sample quantities obtained from a cervicovaginal or buccal swab. Testing can be included during a routine gynecological exam without further discomfort to the patient. The technologies employed in the execution of these tests, Polymerase Chain Reaction (PCR), minisequencing, and liquid microarray detection, combine to form an innovative detection method that allows for the use of smaller sample sizes without compromising sensitivity or specificity. Upon arrival at MDL, samples are processed for genomic DNA extraction. Extracted DNA is then subjected to a multiplex PCR reaction to amplify regions within the appropriate gene(s).

This amplified DNA now serves as the template for the minisequencing portion of the reaction. Minisequencing, also referred to as Single Base Extension (SBE), is a well known method of detection for single nucleotide polymorphisms (SNPs). Primers complementary to regions immediately adjacent to each mutation anneal to the amplified genomic regions and the reaction conditions are such that a single, labeled nucleotide complementary to the genomic template is added to the primer. To determine the identity of the incorporated nucleotide, the assay is divided into four separate reactions which contain either A, T, C or G dideoxynucleotides. Detection is achieved through liquid microarray utilizing beads that are both tagged and fluorescently labeled. Each mutation is assigned one of one hundred fluorescently labeled beads, each having a unique spectral pattern, whose surfaces are coated with a unique tag that is approximately 20 nucleotides long. These beads allow for the analysis of multiple mutations from a single specimen in a single reaction in a manner that is accurate, sensitive and highly specific.

MDL's Ashkenazi Jewish Carrier Screening tests provide a simple, minimally invasive method of determining the carrier status for the nine aforementioned commonly inherited disorders.

Now available on the **OneSwab**[®]:

Test No.	Test/Panel Name
1213	Ashkenazi Jewish Carrier Screening Panel by Bio-Plex Analysis (Canavan Disease, Cystic Fibrosis, Familial Dysautonomia, Tay-Sachs Disease)
1214	Ashkenazi Jewish Carrier Screening Expanded Panel by Bio-Plex Analysis (Bloom Syndrome, Canavan Disease, Cystic Fibrosis, Familial Dysautonomia, Fanconi Anemia Type C, Gaucher Disease, Mucopolipidosis Type IV, Niemann-Pick Disease Type A, Tay-Sachs Disease)
1207	Bloom Syndrome by Bio-Plex Analysis
1209	Canavan Disease by Bio-Plex Analysis
1201	Cystic Fibrosis Genetic Carrier Screening by Bio-Plex Analysis
1210	Familial Dysautonomia by Bio-Plex Analysis
1205	Fanconi Anemia Type C by Bio-Plex Analysis
1211	Gaucher Disease by Bio-Plex Analysis
1212	Mucopolipidosis Type IV by Bio-Plex Analysis
1206	Niemann-Pick Disease Type A by Bio-Plex Analysis
1208	Tay-Sachs Disease by Bio-Plex Analysis