RESULTS RECIPIENT

RESULT MANAGEMENT ENABLED CLINIC
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Report Date: 05/29/2019

FEMALE

ANA LOW
DOB: 09/03/1981
Ethnicity: Northern European
Sample Type: OG-510 Saliva
Date of Collection: 05/24/2019
Date Received: 05/29/2019
Date Tested: 05/29/2019
Barcode: 55200000000334
Indication: Screening for genetic disease carrier status

MALE

N/A

The set of conditions tested by this Foresight Carrier Screen has been modified to align with payor medical policy guidelines. See the 'Conditions Tested' section for details.

Foresight® Carrier Screen

POSITIVE: CARRIER

ABOUT THIS TEST

The **Myriad Foresight Carrier Screen** utilizes sequencing, maximizing coverage across all DNA regions tested, to help you learn about your chance to have a child with a genetic disease.

RESULTS SUMMARY

Risk Details	ANA LOW	Partner
Panel Information	Foresight Carrier Screen ACOG/ACMG/DMD Panel Fundamental Panel Fragile X Syndrome **(14 conditions tested)**	N/A
POSITIVE: CARRIER Cystic Fibrosis **Reproductive Risk: 1 in 110** **Inheritance: Autosomal Recessive**	**CARRIER*** NM_000492.3(CFTR):c.54-5940_273+10250del21kb heterozygote	The reproductive risk presented is based on a hypothetical pairing with a partner of the same ethnic group. Carrier testing should be considered. See "Next Steps".

*Carriers generally do not experience symptoms.

No disease-causing mutations were detected in any other gene tested. A complete list of all conditions tested can be found on page 6.

CLINICAL NOTES

- None

NEXT STEPS

- Carrier testing should be considered for the diseases specified above for the patient's partner, as both parents must be carriers before a child is at high risk of developing the disease.
- Genetic counseling is recommended and patients may wish to discuss any positive results with blood relatives, as there is an increased chance that they are also carriers.

POSITIVE: CARRIER

Cystic Fibrosis

Reproductive risk: 1 in 110
Risk before testing: 1 in 3,000

Gene: CFTR | **Inheritance Pattern:** Autosomal Recessive

Patient	ANA LOW	No partner tested
Result	Carrier	N/A
Variant(s)	NM_000492.3(CFTR):c.54-5940_273+10250del21kb heterozygote	N/A
Methodology	Sequencing with copy number analysis	N/A
Interpretation	This individual is a carrier of cystic fibrosis. Carriers generally do not experience symptoms. Disease phenotype is dependent on, but not necessarily predicted by, the combination of mutations inherited.	N/A
Detection rate	>99%	N/A
Exons tested	NM_000492:1-27.	N/A

What is Cystic Fibrosis?

Cystic fibrosis (CF) is a genetic condition characterized by the production of abnormally thick, sticky mucus, particularly in the lungs and digestive system. While it is normal to have mucus lining the organs of the respiratory, digestive, and reproductive systems in order to lubricate and protect them, in people with CF this mucus is thick and sticky. This abnormal mucus results in the clogging and obstructing of various systems in the body. CF is a chronic condition that worsens over time.

Most people with CF experience breathing problems and frequent lung infections that lead to permanent lung damage such as scarring (fibrosis) and sac-like growths (cysts). The pancreas, an organ that produces insulin and digestive enzymes, is often affected by CF. The sticky mucus caused by CF can block ducts which ferry enzymes from the pancreas to the rest of the body, resulting in problems such as diarrhea, malnutrition, and poor growth. Infertility, particularly in men, and delayed puberty are also common among people with cystic fibrosis.

The severity of symptoms varies from person to person, even among individuals with the same mutations. Most cases of CF are diagnosed in early childhood. However, in general, individuals with two classic mutations are more likely to have a severe form of the disease including problems with the pancreas, while individuals with one classic and one non-classic or individuals with two non-classic mutations are more likely to have a milder form of the condition and may avoid problems with the pancreas.

Mutations in the same gene that causes CF can result in a condition in males called congenital absence of the vas deferens (CAVD). In CAVD, the vas deferens (a reproductive organ involved in sperm transport) is improperly formed, leading to infertility.

How common is Cystic Fibrosis?

According to the National Institutes of Health, CF is the most common deadly inherited condition among Caucasians in the United States. Disease-causing mutations in the CFTR gene are more common in some ethnic populations than others.

Ethnic Group	Carrier Rate	Affected Rate
French Canadian	1 in 16	1 in 900
Caucasian	1 in 28	1 in 3,000
Ashkenazi Jewish	1 in 28	1 in 3,000
Hispanic	1 in 46	1 in 8,300
African American	1 in 66	1 in 17,000
Asian	1 in 87	1 in 30,000

How is Cystic Fibrosis treated?

There is no treatment that addresses the cause of CF, but there are many options to treat the symptoms it produces. Because thick mucus can build up in the respiratory system, it is important to keep the person's airways open in order to ease breathing and prevent infection. This can be accomplished with various prescription drugs as well as by physically loosening mucus by pounding on the person's back in a prescribed way. This treatment, known as "postural drainage and chest percussion" must be performed by someone other than the affected person, and is typically done at least once daily. As respiratory infections occur, physicians typically prescribe antibiotics.

Physicians will also monitor the digestive system to ensure that the person is getting proper nutrition. Enzymes or vitamin supplements may be prescribed. Both the respiratory and digestive systems of a person with CF must be monitored regularly by his or her medical team.

Surgery may be needed to correct certain problems caused by CF. Lung transplants are an option for some people.

What is the prognosis for a person with Cystic Fibrosis?

Thanks to improved treatments and a better understanding of the condition, the average life expectancy for people with CF who live to adulthood is 35 years. Children born with CF today who receive early treatment may live even longer.

Methods and Limitations

ANA LOW [Foresight Carrier Screen]: Sequencing with copy number analysis, triplet repeat detection, spinal muscular atrophy, and analysis of homologous regions.

Sequencing with copy number analysis

High-throughput sequencing and read depth-based copy number analysis are used to analyze the listed exons, as well as selected intergenic and intronic regions, of the genes in the Conditions Tested section of the report. The region of interest (ROI) of the test comprises these regions, in addition to the 20 intronic bases flanking each exon. In a minority of cases where genomic features (e.g., long homopolymers) compromise calling fidelity, the affected intronic bases are not included in the ROI. The ROI is sequenced to high coverage and the sequences are compared to standards and references of normal variation. More than 99% of all bases in the ROI are sequenced at greater than the minimum read depth. Mutations may not be detected in areas of lower sequence coverage. Small insertions and deletions may not be as accurately determined as single nucleotide variants. Genes that have closely related pseudogenes may be addressed by a different method. *CFTR* and *DMD* testing includes analysis for both large (exon-level) deletions and duplications with an average sensitivity of 99%, while other genes are only analyzed for large deletions with a sensitivity of >75%. However, the sensitivity may be higher for selected founder deletions. The breakpoints of copy number variants and exons affected are estimated from probe positions. Only exons known to be included in the copy number variant are provided in the name. In some cases, the copy number variant may be larger or smaller than indicated. If *GJB2* is tested, two large upstream deletions which overlap *GJB6* and affect the expression of *GJB2*, del(*GJB6*-D13S1830) and del(*GJB6*-D13S1854), are also analyzed. Mosaicism or somatic variants present at low levels may not be detected. If detected, these may not be reported.

Detection rates are determined by using literature to estimate the fraction of disease alleles, weighted by frequency, that the methodology is unable to detect. Detection rates only account for analytical sensitivity and certain variants that have been previously described in the literature may not be reported if there is insufficient evidence for pathogenicity. Detection rates do not account for the disease-specific rates of de novo mutations.

All variants that are a recognized cause of the disease will be reported. In addition, variants that have not previously been established as a recognized cause of disease may be identified. In these cases, only variants classified as "likely" pathogenic are reported. Likely pathogenic variants are described elsewhere in the report as "likely to have a negative impact on gene function". Likely pathogenic variants are evaluated and classified by assessing the nature of the variant and reviewing reports of allele frequencies in cases and controls, functional studies, variant annotation and effect prediction, and segregation studies. Exon level duplications are assumed to be in tandem and are classified according to their predicted effect on the reading frame. Benign variants, variants of uncertain significance, and variants not directly associated with the intended disease phenotype are not reported. Curation summaries of reported variants are available upon request.

Triplet repeat detection

PCR is used to size the CGG repeat in the 5' UTR of *FMR1* (NM_002024.4: c.1-131CGG[1_n]). PCR products generated from fluorescently labeled primers are detected by capillary electrophoresis. Reported sizes are accurate to +/- 1 repeat for normal/intermediate alleles and +/-2 repeats for premutation alleles. Alleles above 200 CGG repeats (full mutations), while identified, are not sized. Nearby mutations may interfere with detection of CGG repeat expansions. Deletion of the CGG repeat region and other similar *FMR1* mutations may not be detectable. Methylation is not analyzed. Small degrees of size mosaicism, including gonadal mosaicism, may not be detected as the test has been calibrated to yield results that are equivalent to the results from Southern blot.

Spinal muscular atrophy

Targeted copy number analysis is used to determine the copy number of exon 7 of the *SMN1* gene relative to other genes. Other mutations may interfere with this analysis. Some individuals with two copies of *SMN1* are carriers with two *SMN1* genes on one chromosome and a *SMN1* deletion on the other chromosome. This is more likely in individuals who have 2 copies of the *SMN1* gene and are positive for the g.27134T>G SNP, which affects the reported residual risk; Ashkenazi Jewish or Asian patients with this genotype have a high post-test likelihood of being carriers for SMA and are reported as carriers. The g.27134T>G SNP is only reported in individuals who have 2 copies of *SMN1*.

Analysis of homologous regions

A combination of high-throughput sequencing, read depth-based copy number analysis, and targeted genotyping is used to determine the number of functional gene copies and/or the presence of selected loss of function mutations in certain genes that have homology to other regions. The precise breakpoints of large deletions in these genes cannot be determined, but are estimated from copy number analysis. High numbers of pseudogene copies may interfere with this analysis.

If *CYP21A2* is tested, patients who have one or more additional copies of the *CYP21A2* gene and a loss of function mutation may not actually be a carrier of 21-hydroxylase-deficient congenital adrenal hyperplasia (CAH). Because the true incidence of non-classic CAH is unknown, the residual carrier and reproductive risk numbers on the report are only based on published incidences for classic CAH. However, the published prevalence of non-classic CAH is highest in individuals of Ashkenazi Jewish, Hispanic, Italian, and Yugoslav descent. Therefore, the residual and reproductive risks are likely an underestimate of overall chances for 21-hydroxylase-deficient CAH, especially in the aforementioned populations, as they do not account for non-classic CAH. If *HBA1*/*HBA2* are tested, some individuals with four alpha globin genes may be carriers, with three genes on one chromosome and a deletion on the other chromosome. This and similar, but rare, carrier states, where complementary changes exist in both the gene and a pseudogene, may not be detected by the assay.

Limitations

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. This test is designed to detect and report germline alterations. While somatic variants present at low levels may be detected, these may not be reported. If more than one variant is detected in a gene, additional studies may be necessary to determine if those variants lie on the same chromosome or different chromosomes. The test does not fully address all inherited forms of intellectual disability, birth defects and genetic disease. A family history of any of these conditions may warrant additional evaluation. Furthermore, not all mutations will be identified in the genes analyzed and additional testing may be beneficial for some patients. For example, individuals of African, Southeast Asian, and Mediterranean ancestry are at increased risk for being carriers for hemoglobinopathies, which can be identified by CBC and hemoglobin electrophoresis or HPLC (*ACOG Practice Bulletin No. 78. Obstet.Gynecol. 2007;109:229-37*).

This test was developed and its performance characteristics determined by Myriad Women's Health, Inc. It has not been cleared or approved by the US Food and Drug Administration (FDA). The FDA does not require this test to go through premarket review. This test is used for clinical purposes. It should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. These results are adjunctive to the ordering physician's evaluation. CLIA Number: **#05D1102604**.

Resources

GENOME CONNECT | http://www.genomeconnect.org

Patients can share their reports via research registries such as Genome Connect, an online research registry working to build the knowledge base about genetics and health. Genome Connect provides patients, physicians, and researchers an opportunity to share genetic information to support the study of the impact of genetic variation on health conditions.

SENIOR LABORATORY DIRECTOR

Jack Ji, PhD, FACMG

PLACEHOLDER E-SIGNATURE

Conditions Tested

Alpha Thalassemia - **Genes:** HBA1, HBA2. Autosomal Recessive. Analysis of homologous regions. **Variants (13):** -(alpha)20.5, --BRIT, --MEDI, --MEDII, --SEA, --THAI/--FIL, -alpha3.7, -alpha4.2, HBA1+HBA2 deletion, Hb Constant Spring, anti3.7, anti4.2, del HS-40. **Detection Rate:** Unknown due to rarity of disease.
Bloom Syndrome - **Gene:** BLM. Autosomal Recessive. Sequencing with copy number analysis. **Exons:** NM_000057:2-22. **Detection Rate:** Northern European >99%.
Canavan Disease - **Gene:** ASPA. Autosomal Recessive. Sequencing with copy number analysis. **Exons:** NM_000049:1-6. **Detection Rate:** Northern European 98%.
Cystic Fibrosis - **Gene:** CFTR. Autosomal Recessive. Sequencing with copy number analysis. **Exons:** NM_000492:1-27. IVS8-5T allele analysis is only reported in the presence of the R117H mutation. **Detection Rate:** Northern European >99%.
Dystrophinopathy (Including Duchenne/Becker Muscular Dystrophy) - **Gene:** DMD. X-linked Recessive. Sequencing with copy number analysis. **Exons:** NM_004006:1-79. **Detection Rate:** Northern European >99%.
Familial Dysautonomia - **Gene:** IKBKAP. Autosomal Recessive. Sequencing with copy number analysis. **Exons:** NM_003640:2-37. **Detection Rate:** Northern European >99%.
Fanconi Anemia, FANCC-related - **Gene:** FANCC. Autosomal Recessive. Sequencing with copy number analysis. **Exons:** NM_000136:2-15. **Detection Rate:** Northern European >99%.
Fragile X Syndrome - **Gene:** FMR1. X-linked Dominant. Triplet repeat detection. **Variant (1):** FMR1 CGG repeat number. **Detection Rate:** Northern European >99%.
Gaucher Disease - **Gene:** GBA. Autosomal Recessive. Analysis of homologous regions. **Variants (10):** D448H, D448V, L483P, N409S, R502C, R502H, R535H, V433L, c.115+1G>A, c.84dupG. **Detection Rate:** Northern European 60%.
Hb Beta Chain-related Hemoglobinopathy (Including Beta Thalassemia and Sickle Cell Disease) - **Gene:** HBB. Autosomal Recessive. Sequencing with copy number analysis. **Exons:** NM_000518:1-3. **Detection Rate:** Northern European >99%.
Hexosaminidase A Deficiency (Including Tay-Sachs Disease) - **Gene:** HEXA. Autosomal Recessive. Sequencing with copy number analysis. **Exons:** NM_000520:1-14. **Detection Rate:** Northern European >99%.
Mucolipidosis IV - **Gene:** MCOLN1. Autosomal Recessive. Sequencing with copy number analysis. **Exons:** NM_020533:1-14. **Detection Rate:** Northern European >99%.
Niemann-Pick Disease, SMPD1-associated - **Gene:** SMPD1. Autosomal Recessive. Sequencing with copy number analysis. **Exons:** NM_000543:1-6. **Detection Rate:** Northern European >99%.
Spinal Muscular Atrophy - **Gene:** SMN1. Autosomal Recessive. Spinal muscular atrophy. **Variant (1):** SMN1 copy number. **Detection Rate:** Northern European 95%.

Risk Calculations

Below are the risk calculations for all conditions tested. Since negative results do not completely rule out the possibility of being a carrier, the **residual risk** represents the patient's post-test likelihood of being a carrier and the **reproductive risk** represents the likelihood the patient's future children could inherit each disease. These risks are inherent to all carrier screening tests, may vary by ethnicity, are predicated on a negative family history and are present even after a negative test result. Inaccurate reporting of ethnicity may cause errors in risk calculation. The reproductive risk presented is based on a hypothetical pairing with a partner of the same ethnic group.

†Indicates a positive result. See the full clinical report for interpretation and details.

Disease	ANA LOW Residual Risk	Reproductive Risk
Alpha Thalassemia	Alpha globin status: aa/aa.	Not calculated
Bloom Syndrome	< 1 in 50,000	< 1 in 1,000,000
Canavan Disease	1 in 9,700	< 1 in 1,000,000
Cystic Fibrosis	NM_000492.3(CFTR):c.54-5940_273+10250del21kb heterozygote †	1 in 110
Dystrophinopathy (Including Duchenne/Becker Muscular Dystrophy)	Not calculated	Not calculated
Familial Dysautonomia	< 1 in 50,000	< 1 in 1,000,000
Fanconi Anemia, FANCC-related	< 1 in 50,000	< 1 in 1,000,000
Fragile X Syndrome	Normal: 29 and 31 repeats	Not calculated
Gaucher Disease	1 in 280	1 in 120,000
Hb Beta Chain-related Hemoglobinopathy (Including Beta Thalassemia and Sickle Cell Disease)	1 in 3,100	1 in 390,000
Hexosaminidase A Deficiency (Including Tay-Sachs Disease)	1 in 30,000	< 1 in 1,000,000
Mucolipidosis IV	< 1 in 50,000	< 1 in 1,000,000
Niemann-Pick Disease, SMPD1-associated	1 in 25,000	< 1 in 1,000,000
Spinal Muscular Atrophy	SMN1: 2 copies 1 in 630	1 in 87,000