Foresight®

Carrier Screen

Executive Summary

Equitable Carrier Screening (ECS) identifies couples who are at risk of passing down serious heritable conditions to their child. These conditions have various outcomes: cognitive or physical impairment, shortened life expectancy, and infant death. Some conditions benefit from early intervention, while others have limited or no treatment options. Traditionally, carrier screening was recommended for certain disorders for patients based on ethnicity and/or family history. However, over time ethnicity-based screening has become less effective as patients are increasingly unable to accurately report their ethnicity leading to a failure of identifying risk for serious genetic disorders that could benefit from early identification and intervention.

Equitable Carrier Screening offers the benefit of testing via full sequencing for many genetic conditions at once. The Myriad Genetics Foresight® Carrier Screen screens for more than 175 genes with a single blood or saliva sample. Approximately 1 in 300 pregnancies is affected by one of the conditions in the Foresight panel – the total risk of serious disorders identified through our panel is higher than the incidence of Down Syndrome and neural tube defects.[1]

- **Screens for 175+ genes, many with >99% accuracy.**[3] Foresight detects couples at-risk for serious, prevalent, and clinically-actionable conditions through advanced technologies including full-exon sequencing and panel-wide deletion calling.
- **Empowers patients with information.** Research demonstrates that ECS impacts the decisions in the majority of at-risk couples: 77% of couples screened preconceptionally and found to be at risk of having a child affected with a serious condition pursued alternative reproductive choices.[4]
- **Is cost-effective relative to conventional screening.** Advances in genomic technologies have enabled an increase in panel size without a corresponding increase in testing cost, making it economical compared to minimal screening.[5]

Test Description

Foresight requires a blood or saliva sample from each individual/donor. Females are typically screened first, but it is strongly encouraged that both partners and/or donors be screened to provide the most accurate picture of a couple's risk.

Detection rates of >99% for the vast majority of genes across all ethnicities are achieved through innovative technology that includes:

- Full-exon sequencing, which provides a significant advantage over targeted sequencing in identifying carriers
- Panel-wide deletion calling, with select duplication analysis to further boost sensitivity
- Real-time curation combining automation with manual investigation to classify variants
- Custom assays for prevalent, technically-challenging and difficult-to-sequence genes

Intended Use Population

Foresight is intended for those planning to start a family, before or during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) recommends that carrier screening and counseling should ideally be performed before pregnancy.[6] Since 1 in 22 couples were identified as at-risk for having a child affected with a serious and actionable condition, the pre-conception period is the preferred time to perform ECS.[3] For couples who are already pregnant, Foresight results may provide reassurance or the advance knowledge to help make decisions about next steps. This may include further diagnostic testing, speaking to a specialist, or developing a care plan to manage newborns with inherited conditions.

Analytical Validity

In 2018, an analytical validation was published assessing the performance of Foresight which demonstrated >99% analytical sensitivity and >99% analytical specificity. Of 7,498 couples screened, 335 (1 in 22) were found to be at risk for an affected pregnancy, underscoring the clinical importance of the test. The authors concluded that ECS provides reliable and affordable risk assessment for many serious recessive and X-linked diseases simultaneously, and validated high-fidelity identification of variant types – especially for diseases with complicated molecular genetics – maximizing at-risk couple detection.[3] (See Table 1.)

Table 1. Foresight® ECS panel

Disease genes	Methodology	Variants reported
General ECS:		
216 genes	NGS	Novel pathogenic SNVs, indels, large deletions
CFTR	NGS	Novel pathogenic SNVs, indels, large deletions, and duplications
DMD	NGS	Novel pathogenic SNVs, indels, large deletions, and duplications
11 genes	NGS	Targeted pathogenic mutations[a]
Technically challenging genes:		
SMN1	NGS	Exon 7 copy number, g.27134T>G SNP
CYP21A2	NGS	Classical: CYP21A2 30-kb deletion, CYP21A2 duplication, CYP21A2 triplication, c.293–13C>G, p.G111Vfs*21, p.I173N, p.[I237N;V238E;M240K], p.L308Ffs*6, p.Q319*, p.Q319* + CYP21A2dup, p.R357W
		Nonclassical: p.P31L, p.V281L
HBA1/2	NGS	Single deletions: -alpha3.7, -alpha4.2
		Double deletions: -(alpha)20.5, - -BRIT, - -MEDI, - -MEDII, - -SEA, - -THAI, or - -FIL
		Frequent SNV: Hb constant spring
		Regulatory deletion: ΔHS-40
		(combinations of most variants above with other deleterious variants or duplications can also be detected)
GBA	NGS	p.N370S, p.D409V, p.D448H, IVS2 + 1G>A, p.L444P, p.R463C, p.R463H, p.R496H, p.V394L, p.L29Afs*18
FMR1	PCR/CE[b]	Number of CGG repeats in the 5'-UTR

a See Table 1 in the online Data Supplement.
b CE, capillary electrophoresis; UTR, untransb lated region.

Clinical Validity

Our team of genetic experts applied a systematic design method to more than 650 genes before selecting the 176 genes included on Foresight. Panel design was based upon clinical significance with diseases prioritized based on the criteria below.[7]

- **Severity:** Is this condition mild, moderate, severe, or profound?
- **Sensitivity:** Ensure near 100% specificity using carefully designed assay and curation protocols.
- **Actionability:** Does this information help patients make decisions?
- **Prevalence:** Is this condition common enough to be of value?

A validated and previously published algorithm that classifies diseases into four severity categories was applied to the genes on Foresight to demonstrate that >99% of the genes were classified as moderate, severe, or profound.[8] Additionally, a standardized framework, known as the Clinical Genome Resource (ClinGen), for evaluation of gene-disease association was used to assess clinical validity of conditions screened. This assessment demonstrated that all genes on Foresight revealed strong evidence of gene-disease association.[9]

Clinical Utility

When at risk couples are identified, 77% of those screened preconceptionally by ECS and found to be at risk of having a child with a serious genetic condition pursued alternative reproductive actions such as prenatal diagnosis, IVF with preimplantation genetic testing or adoption. Among those screened during pregnancy, 37% pursued or planned for prenatal diagnosis.[4] Additionally, 86% of affected pregnancies detected by ECS are missed when screening is done for cystic fibrosis and spinal muscular atrophy alone, missing the opportunity to act upon early identification.[10]

Medical Society Guidelines

In 2021 American College of Medical Genetics and Genomics (ACMG) announced in their Practice Resource, “Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG)” from Gregg, et al. that they recommend “... a consistent and equitable approach for offering carrier screening to all individuals during pregnancy or preconception,” comprising of a pan-ethnic panel of a minimum of ninety-seven, serious, autosomal recessive and X-linked conditions. Additionally, this particular Practice Resource “aims to improve the implementation of carrier screening allowing diverse populations to benefit from new and emerging genomic technologies.

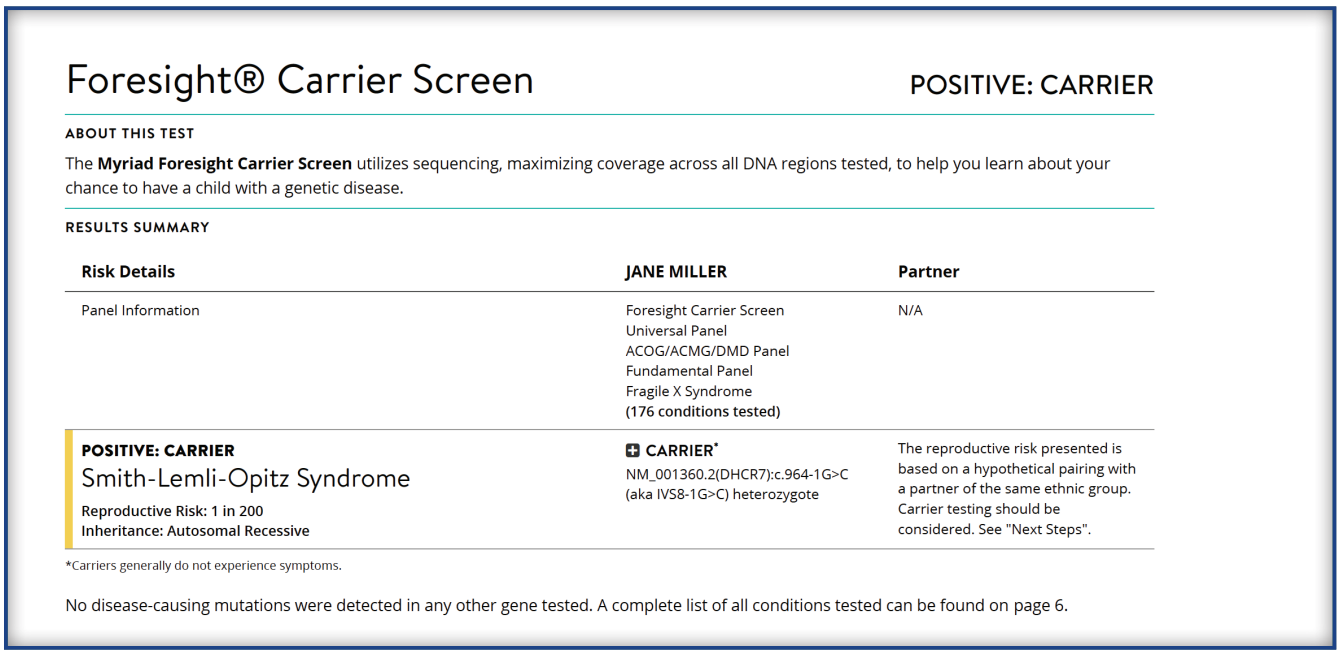
The American College of Obstetricians and Gynecologists (ACOG) also recognizes carrier screening as an acceptable strategy that can improve outcomes for patients. In a joint commentary, ACOG, ACMG, the National Society of Genetic Counselors (NSGC), the Society for Maternal Fetal Medicine (SMFM) and the Perinatal Quality Foundation (PQF) note that carrier screening can provide information about carrier status beyond population estimates and eliminates the need for ethnicity-based screening.[13]

Health Economics

While ECS provides couples with information to optimize pregnancy outcomes based on their personal values and preferences, the cost-effectiveness of the screen has also been demonstrated.[13] Advances in genomic testing technology, such as next generation sequencing (NGS), have enabled increased panel size without a corresponding increase in testing cost, making ECS more efficient than single-gene screening. Compared to minimal screening, preconception ECS is a cost-effective way to reduce the affected birth rate due to the high intervention rate (77%) among at-risk couples.[4,5]

ECS can also help patients, physicians, and payers avoid lengthy and expensive diagnostic journeys, by providing information that can spur early intervention and treatment for an affected child. On average, it takes 6 – 8 years to accurately diagnose a rare genetic condition.[14] Pregnancies affected with a disease identified through ECS incur, on average, $1.1MM in lifetime costs.[5]

Sample reports



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	JANE MILLER	Partner
Panel Information	Foresight Carrier Screen Universal Panel ACOG/ACMG/DMD Panel Fundamental Panel Fragile X Syndrome **(176 conditions tested)**	N/A
POSITIVE: CARRIER Smith-Lemli-Opitz Syndrome **Reproductive Risk: 1 in 200** **Inheritance: Autosomal Recessive**	**CARRIER*** NM_001360.2(DHCR7):c.964-1G>C (aka IVS8-1G>C) 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.

POSITIVE: CARRIER

Smith-Lemli-Opitz Syndrome

Reproductive risk: 1 in 200
Risk before testing: 1 in 9,800

Gene: DHCR7 | **Inheritance Pattern:** Autosomal Recessive

Patient	**JANE MILLER**	**No partner tested**
Result	✚ Carrier	N/A
Variant(s)	NM_001360.2(DHCR7):c.964-1G>C(aka IVS8-1G>C) heterozygote	N/A
Methodology	Sequencing with copy number analysis	N/A
Interpretation	This individual is a carrier of Smith-Lemli-Opitz syndrome. Carriers generally do not experience symptoms. The c.964-1G>C mutation is associated with the severe form of this disease.	N/A
Detection rate	>99%	N/A
Exons tested	NM_001360:3-9.	N/A

1. National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention (CDC). "Data & Statistics on Birth Defects." 2020. Retrieved from: www.cdc.gov/ncbddd/birthdefects/data.html **2.** Beauchamp KA, et al. Genet Med. 2019;21(11):2569-2576. **3.** Hogan GJ, et al. Clin Chem. 2018;64(7):1063-1073. **4.** Johansen Taber KA, et al. Genet Med. 2019;21(5):1041-1048. **5.** Beauchamp KA, et al. Genet Med. 2019;21(9):1948-1957. **6.** American College of Obstetrics and Gynecologists Committee on Genetics. Committee Opinion No. 690: Carrier screening in the age of genomic medicine. Obstet Gynecol. 2017:129:e35-40. **7.** Beauchamp KA, et al. Genet Med. 2018;20(1):55-63. **8.** Arjunan A, et al. Prenatal Diagnosis. 2020: 1-12. doi:10.1002/pd.5762. **9.** Balzotti M, et al. Hum Mutat. 2020 Aug;41(8):1365-1371. **10.** Haque IS, et al. Modeled fetal risk of genetic diseases identified by expanded carrier screening. JAMA. 2016; 316(7):734-742. doi:10.1001/ jama.2016.11139. **11.** Watson MS, et al. Genet Med. 2004;6(5):387-391. **12.** Prior TW. Professional Practice and Guidelines Committee. Carrier screening for spinal muscular atrophy. Genet Med. 2008;10(11):840-842 **13.** Edwards JG, et al. Obstet Gynecol. 2015;125(3):653-662. **14.** Global Genes. July 2020. Rare Facts. Retrieved from: www.globalgenes.org/rare-facts **15.** Gregg AR, et al. Genet Med. 2021 Jul 20. doi: 10.1038/s41436-021-01203-z.

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