EXECUTIVE SUMMARY

Carrier screening 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.

Expanded carrier screening (ECS) offers the benefit of testing via full sequencing for many genetic conditions at once. The Foresight® Carrier Screen from Myriad Genetics, Inc., 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.

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
EXECUTIVE SUMMARY

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. 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. 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. (See Table 1.)

CLINICAL VALIDITY
Our team of genetic experts applied a systemic 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.

- **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. 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.

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. 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.

MEDICAL SOCIETY GUIDELINES
The American College of Obstetricians and Gynecologists (ACOG) and the American College of Genetics and Genomics (ACMG) recommend cystic fibrosis and spinal muscular atrophy screening for all women who are considering pregnancy or are already pregnant. ACOG also recognizes ECS as an acceptable screening 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 ECS can provide information about carrier status beyond population estimates and eliminates the need for ethnicity-based screening.

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. 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.

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. Pregnancies affected with a disease identified through ECS incur, on average, $1.1MM in lifetime costs.

TEST REPORT
The Foresight report offers clear, insightful, and actionable information in a way that can be easily absorbed by patients and assist in decision making. Test results can be securely accessed online by both your physicians and members. Myriad Complete provides automated results delivery and tracking, test reports, and on-demand genetic counseling. This online service allows physicians to seamlessly integrate testing into their practices benefiting their patients’ care.
REFERENCES