Commonly Screened Disorders

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Cystic fibrosis (CF), the most common autosomal recessive inherited disorder, affects the epithelia of several organs, resulting in respiratory and gastrointestinal complications. The clinical presentation varies, from isolated nasal polyps or isolated congenital bilateral absence of the vas deferens (CBAVD), to classic CF, with an infancy/childhood onset, severe respiratory complications, pancreatic insufficiency, and a shortened life expectancy. While there are treatments for some of the symptoms of CF, there is currently no cure.

Genetics: CF is an autosomal recessive disorder with some genotype / phenotype correlation; however, most mutations are not associated with a specific clinical presentation.

Spinal muscular atrophy (SMA), the leading genetic cause of death in children under the age of 2, is a neuromuscular disorder characterized by muscular atrophy, weakness, and pulmonary and growth complications. Onset ranges from prenatal through young-adulthood and clinical severity varies accordingly. Lifespan correlates with age of onset; for the most common (also more severe) form, lifespan is typically less than 2 years due to respiratory failure. There is currently no cure for SMA. Treatment centers around the management of symptoms.

Genetics: SMA is an autosomal recessive disorder. The majority of disease (95-98%) is due to a deletion of exon 7 in the *SMN1* gene. The remaining 2-5% is due to other types of mutations in *SMN1*. 2% of disease alleles are *de novo* (new in the affected individual, not inherited from a parent). Copy number of a neighboring pseudogene, *SMN2,* may affect the clinical severity of the disease.

Fragile X syndrome, the most common form of inherited intellectual disability, is characterized by developmental delays, moderate intellectual disability, a characteristic appearance, and autistic-like behaviors. Management of the disorder typically includes early intervention, individualized education plans, and individualized treatment of other manifestations as appropriate. Of note, carriers of premutations (50-200 repeats) may experience symptoms of fragile-X associated tremor ataxia syndrome (FXTAS) or fragile-X associated premature ovarian insufficiency (FXPOI).

Genetics: Fragile X syndrome is an X-linked disorder that is more common in males, however females may also present with clinical features. Over 99% of fragile X syndrome is due to an increased number of GCC repeats (typically > 200 CGG repeats) in the *FMR1* region.

Resources: GeneReviews for *CFTR*, *SMN1*, and *FMR1*, respectively. Http://www.ncbi.nlm.nih.gov/sites/GeneTests/review

Carrier Screening at a Glance

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Carrier screening

Carrier screening is used to assess an individual's, and ultimately, a couple's, risk of having a child with a serious genetic disorder. Both the American Congress of Obstetricians & Gynecologists (ACOG) and the American College of Medical Genetics (ACMG) publish carrier screening recommendations. These recommendations are based on an individual's/couple's ethnicity and family history.

All people carry a number of disease-causing mutations for severe genetic disorders. However the vast majority of these disorders are so infrequent that the likelihood of their partner also being a carrier of the same disorder is exceedingly rare. Population carrier screening for these rare disorders has low clinical utility and is not recommended by ACOG or ACMG.

Implications of a negative result

A negative carrier screen reduces the risk that the individual screened is a carrier of the disorder(s) tested. While the goal is to significantly reduce the likelihood that an individual is a carrier, no carrier screen completely eliminates that risk and there is always some residual risk of being a carrier.

Implications of a positive result

A positive carrier screen indicates that a disease-causing mutation has been identified in the individual tested. Carriers typically do NOT have health complications related to their carrier status. A carrier, however, is at increased risk to have a child with the disorder they carry. Testing of their reproductive partner will provide the best assessment of this risk. If both partners are known carriers of the same disease, regardless of the mutation they carry, each pregnancy is at a 25% risk to be affected with the disorder.