Cystic Fibrosis 139-Variant Assay

**Background**

Cystic fibrosis (CF) (OMIM#219700) is a multisystem genetic disease of sodium chloride transport that commonly involves the lungs, pancreas, intestines, liver, sweat glands and male reproductive system. Respiratory failure is the leading cause of death among individuals with CF, with median life expectancy of 41 years (CF Foundation). CF is one of the most common inherited conditions among Caucasians and is diagnosed in approximately 1 in 3,000 individuals. The condition is less common but does occur among all other racial groups. CF has an autosomal recessive inheritance pattern and heterozygous mutation carriers (1 in 25-30 Caucasians) are unaffected. If both partners in a couple are mutation carriers, there is a 25% chance for each child to have CF and a 50% chance for each child to be a carrier.

The cystic fibrosis transmembrane conductance regulator (CFTR) gene was isolated in 1989. The most common pathogenic variant, F508del, was identified in the same year and represents 70% of CF mutations among Caucasians. To date, more than 1,800 gene variants have been found, though most are quite rare. Mutations in CFTR have also been identified in individuals with atypical presentations, such as acute or chronic recurrent pancreatitis and isolated congenital absence of vas deferens (CAVD), as well as in individuals with late-onset or mild CF symptoms.

**Clinical Indications**

**Carrier Screening**

In order to identify couples at risk of having a child with CF, both the American College of Medical Genetics and the American College of Obstetricians and Gynecologists recommend that CF carrier screening be offered routinely to women of reproductive age. Mutation screening should include the pan-ethnic panel of the 23 most common CFTR pathogenic variants.

**Diagnostic Testing**

In both pediatric and adult patients in whom CFTR-related disorders are suspected, genetic testing is routinely performed as an initial diagnostic test or as confirmation of clinical findings, or sweat chloride testing, which remains the standard diagnostic test.

Newborn screening (NBS) for cystic fibrosis is now offered universally in the United States through each state’s mandatory NBS program. Initial screening measures a digestive enzyme, immunoreactive trypsinogen (IRT). Because elevations in IRT may have other causes, a CFTR mutation analysis is often performed as a secondary screen, though this varies by state. Since the advent of routine carrier screening and NBS, many individuals with CF are recognized at, or even before, birth.

**Methodology**

The Illumina MiSeqDx™ Cystic Fibrosis 139-Variant Assay is a qualitative in vitro diagnostic system used to simultaneously detect 139 clinically relevant cystic fibrosis disease-causing mutations and variants of the cystic fibrosis transmembrane conductance regulator (CFTR) gene in genomic DNA isolated from human peripheral whole blood. The assay is designed to identify a specific subset of known variants in the CFTR gene, but does not include all variants identified in the CFTR gene. Therefore, the failure to identify a variant does not guarantee that other CFTR variants are not present in the samples being analyzed.

**Mutations Detected**

The sequence changes reported by the Cystic Fibrosis 139-Variant Assay were specifically chosen because they represent the full set of clinically validated variants classified as CF-causing in the CFTR2 database at Johns Hopkins University, a product of the CFTR2 (Clinical and Functional Translation of CFTR) initiative. The assay tests for: 134 CF-causing mutations; one ACMG recommended panel variant (R117H, classified as a Mutation of Varying Clinical Consequence, MVCC, by CFTR2); one conditionally reported modifying variant (PolyTG/PolyT); and three conditionally reported benign variants (I506V, I507V, F508C) for a total of 139 reported sequence changes.
Interpretation

Thorough interpretation is dependent on the indication for testing and relies on good communication of clinical information from the ordering provider.

Results should be used and interpreted in the context of a full clinical evaluation. The assay does not include all sequence changes identified in the CFTR gene. Therefore, the failure to identify a variant does not guarantee that other CFTR variants are not present in the samples being analyzed. Variants identified by this assay vary in frequency among different populations. As with any hybridization-based assay, underlying variants in oligonucleotide-binding regions can affect the alleles being probed and, consequently, the calls made. The orientation of the PolyTG/PolyT variant, whether in cis/trans to the R117H variant, cannot be ascertained. PolyTG/PolyT are homopolymeric regions known to be difficult to interpret with sequence-based assays due to polymerase slippage. A 0.9% (4/448) miscall rate is reported for PolyTG/PolyT results.

Due to the complex issues surrounding cystic fibrosis, documented informed consent and genetic counseling is recommended for all individuals undergoing testing.

References


Additional Resources


Illumina, Inc. 2014. MiSeqDx™ Cystic Fibrosis 139-Variant Assay, Part # 15038347 Rev. A.
## Test Overview

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<thead>
<tr>
<th>Test Name</th>
<th>Cystic Fibrosis 139-Variant Assay</th>
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<td>Ordering Mnemonic</td>
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