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Guide to Carrier Screening for Cystic Fibrosis

by Kristen Champion, Ph.D., FACMG
med fusion, Technical Director, Molecular Pathology

What is Cystic Fibrosis?

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive condition in the non-Hispanic white population. It is a progressive, multisystem disease that primarily affects the pulmonary, pancreatic, and gastrointestinal systems but does not affect intelligence. The current median survival is approximately 37 years, with respiratory failure as the most common cause of death. Cystic fibrosis is caused by mutations in the CF transmembrane regulator (CFTR) gene, located on chromosome 7. Two copies of deleterious mutations in this gene cause CF. The disease incidence is 1 in 2,500 individuals in the non-Hispanic white population and considerably less in other ethnic groups.

Carrier Screening for Cystic Fibrosis: who should get it and why?

Pre-conception and prenatal cystic fibosis carrier screening should be made available to all women of reproductive age as a routine part of obstetric care, according to a revised Committee Opinion issued by The American College of Obstetricians and Gynecologists (ACOG)[1]. Prenatal and pre-conception carrier screening for CF was introduced into routine obstetric practice in 2001. The goal of CF carrier screening is to identify couples at risk of having a child with classic CF. Cystic fibrosis is more common among the non-Hispanic white population compared with other racial and ethnic populations; however, it is becoming increasingly difficult to assign a single ethnicity to affected individuals. It is reasonable, therefore, to offer CF carrier screening to all patients regardless of ethnicity[1]. The sensitivity of the screening test varies among different ethnic groups, ranging from less than 50% in those of Asian ancestry to 94% in the Ashkenazi Jewish population. Therefore, screening is most efficacious in non-Hispanic white and Ashkenazi Jewish populations. Because testing is offered for only the most common mutations, a negative screening test result reduces, but does not eliminate, the chance of being a CF carrier and having an affected offspring. Therefore, if a patient is screened for CF and has a negative test result, she still has a residual risk of being a carrier. The most common CF carrier frequencies as well as the rates of residual carrier risk after a negative test result are listed by racial and ethnic group in Table 1.

Table 1:

Ethnicity	Prior Carrier Risk	Residual Carrier Risk after Negative Screen with med fusion 32 Mutation Panel*	Residual Carrier Risk after Negative Screen with Quest CFvantage 155 Mutation Panel**	Improvement of Residual Carrier Risk with 155 Mutation Panel over 32 Mutation Panel
Ashkenazi Jewish	1/24 (4.16%)	1/385 (0.26%)	1/461 (0.22%)	0.04%
Non-Hispanic Caucasian	1/25 (4.00%)	1/200 (0.50%)	1/241 (0.41%)	0.09%
Hispanic American	1/46 (2.17%)	1/165 (0.61%)	1/376 (0.27%)	0.34%
African American	1/65 (1.54%)	1/205 (0.49%)	1/292 (0.34%)	0.15%
Asian American	1/94 (1.06%)	1/185 (0.54%)	1/199 (0.50%)	0.04%

*Residual risk estimates are based on the ACMG/ACOG-recommended 23 mutation panel. The additional mutations detected with this essay are not expected to have a significant effect on the overall detection rates.

**Residual risk estimates are based on a subset of 78 mutations detectable by the panel, including the 23 ACMG/ACOG-recommended mutations; exact data are currently unavailable for all 155 mutations in the CFvantage Cystic Fibrosis Expanded Screen.

The decision to have CF carrier screening should be reached by informed choice. Patients should receive information about CF and its inheritance pattern. It is important for patients and their partners to recognize the sensitivity and limitations of testing as well as their reproductive options.

Which Mutations Should be Included in Routine Carrier screening?

To date, more than 1,700 mutations have been identified for CF. The initial American College of Medical Genetics Cystic Fibrosis Carrier Screening Working Group recommended that laboratories use a pan-ethnic panel of 25 mutations that were present in at least 0.1% of patients with classic CF[2]. Current guidelines, revised by the American College of Medical Genetics in 2004 (and reaffirmed in 2013), use a 23-mutation panel and were developed after assessing the initial experiences upon implementation of CF screening into clinical practice[3]. A study sponsored by a large commercial reference laboratory in the U.S. and published in 2011 in the Journal Genetics in Medicine evaluated the performance of population-based carrier screening in the U.S. and compared the observed detection rates with the predicted rates of the ACMG-recommended panel of 23 mutations[4]. They reviewed approximately 3 million cystic fibrosis screening tests, 1300 prenatal diagnostic tests, and 2400 cystic fibrosis sequencing analyses. They concluded that the ACMG-recommended panel of 23 mutations was performing as predicted in detecting cystic fibrosis carriers in the U.S. among all ethnic groups and that no recurrent mutations were detected in sufficient numbers to justify including any additional mutations to the existing panel, and stated that an expanded mutation panel would have a minimal impact on the prevention of births of children affected with cystic fibrosis.

What is the harm in screening for more than the recommended mutations?

Performing CF screening for more than the 23 common mutations may be harmful. Many of the rare CFTR gene variations reported have little evidence to indicate whether they are serious, mild, or have any clinical significance at all. Therefore, performing routine population screening for additional rare mutations is not advised by the ACOG or ACMG, especially since individuals often make irreversible reproductive decisions based on their presence and the assumption that all CF gene variations cause classic CF disease. Routine carrier screening of healthy individuals should include only common mutations that are clearly associated with CF. The inclusion of other rare variations in the screening panel is risky.

Several CLIA-certified commercial laboratories now offer expanded CF carrier screening panels which may screen for 100 or more mutations. The benefits of these expanded panels may be over-emphasized or exaggerated in marketing materials. In actuality, the residual carrier risk after screening negative for an expanded mutation panel versus the ACMG 23 mutation panel only improves by a modest amount (see table 1). For an individual of Caucasian ethnicity the residual risk only improves from 1/200 (0.50%) after a negative screen with a 23 mutation panel to about 1/241 (0.41%) after a negative screen with a 155 mutation panel. In addition, expanded mutation panels often include variants with unknown or uncertain evidence of pathogenicity, which may lead to couples having unnecessary amniocentesis procedures (which carry a significant risk of miscarriage) and subsequently to laboratories receiving requests to perform testing on fetal samples where one parent carries a classic CF mutation and the other carries a variant of uncertain or even likely benign significance. This scenario can cause great confusion and uncertainty to expectant parents who may make poorly informed reproductive decisions based on incorrect assumptions (please see publication entitled “The dangers of including non-classical cystic fibrosis variants in population-based screening panels: p.L997F, further genotype/phenotype correlation data”. Strom et al. Genetics in Medicine, December 2015).

The CFTR2 Project: Improving genetic testing for cystic fibrosis

The CFTR2 project is a recent initiative by the Cystic Fibrosis Foundation, Johns Hopkins School of Medicine and Sequenom Laboratories to create a publicly available resource that provides information about the clinical and functional translation of specific CFTR mutations. The goal of the project is to increase the fraction of variants in the CFTR gene that have been assessed for their propensity to cause disease in order to improve genetic testing and clinical care for cystic fibrosis. At the initiation of the project only 23 variants were defi ned as disease causing. Combining phenotypic evidence with functional analysis collected from over 39,000 individuals who were enrolled in registries and clinics around the world has enabled unambiguous assignment of pathogenicity to an additional 104 variants and counting[6]. The availability of this exciting resource will enable diagnostic laboratories to design and offer CF carrier screening tests which only include functionally validated and clinically relevant cystic fibrosis variants and to improve detection rates within demographically diverse populations.

CF carrier screening tests offered by med fusion

med fusion currently offers a 32 mutation carrier screening test which includes the 23 mutations recommended by the American College of Medical Genetics (ACMG, 2004) and the American College of Obstetricians and Gynecologists (ACOG, 2005) plus additional rare multiethnic mutations. This test also includes automatic reflex testing for the 5T allele in intron 8 for patients that are positive for the R117H mutation as recommend by the ACMG. This panel does not include variant alleles for which a definitive prediction of clinical outcome cannot be provided or variants which are known to be associated with a mild or uncertain phenotype.

med fusion is currently in the process of developing an expanded mutation screening panel for CF based on data from the CFTR2 project. This panel will only include functionally validated and clinically relevant cystic fibrosis variants in order to provide our patients with a high quality and clinically appropriate expanded carrier screening option.

References:

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3. Watson et al. Cystic Fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genetics in Medicine, 6 (4), September/October 2004.
4. Strom et al. Cystic fibrosis testing 8 years on: Lessons learned from carrier screening and sequencing analysis. Genetics in Medicine, 13 (2), February 2011.
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