MEDCO FORUM®

PRESENTING INNOVATIVE PRODUCTS & SERVICES TO HEALTHCARE PROFESSIONALS

VOLUME 13 NUMBER 33 AUGUST 2006

REPRINT

GENETIC SCREENING FOR CARRIERS OF THE CYSTIC FIBROSIS GENE

The American College of Obstetricians and Gynecologists (ACOG) currently recommends a panel of 23 mutations as the standard of care for cystic fibrosis (CF) carrier screening. These recommendations were issued in 2004, following a study that recommended removal of two mutations included in the original 2001 guidelines of ACOG and the American College of Medical Genetics (ACMG) (*1*,*2*).

CF Carrier Screening is Effective with 23 Mutations and Meets Standard of Care

As of June 2006, nearly 1,500 variants of the CFTR (cystic fibrosis transmembrane conductance regulator) gene have been discovered (*3*). The vast majority of these variations, however, display no clear association with the disease. In devising the panel of mutations for population-based carrier screening, the ACOG, in collaboration with the ACMG, considered a number of factors, including: the solidity of evidence linking specific mutations to CF; the varying frequencies of particular mutations among ethnic groups; and the heterogeneity of the U.S. population. The ACOG developed the panel of 23 mutations given in Table 1 (*1*,*2*).

This panel is considered the standard of care for the pan-ethnic population present in the U.S. It recognizes both the higher prevalence of CF in Caucasian and Ashkenazi Jewish populations and the predominant mutations found in other ethnic groups. The data in Table 2 (*4*) demonstrate residual risk to the fetus across a variety of ethnic groups when the ACOG/ ACMG panel is used for screening.

Testing for mutations in addition to the core panel of 23 would have a minimal effect on residual risk. For example, using the 23-mutation core panel, a non-Hispanic Caucasian couple both negative for CF would have a 1:207,000 residual risk to the fetus; if 20 more mutations were added[1], the risk would decrease to 1:222,000. Likewise, residual risk for Asian American couples would be reduced from 1:125,000 to 1:156,000; for Hispanic Americans, from 1:125,000 to 1:166,000; and for African American couples, from 1:176,000 to 1:188,000 (*6*). Since changes to margins of risk this small are unlikely to influence decisions couples make regarding pregnancy, the clinical utility of adding more mutations is likely to be negligible and not the recommended standard of care of ACOG/ ACMG.

Testing for additional mutations can, in fact, create opportunity for error and confusion. Many of the polymorphisms identified in the CFTR gene have not been found to play a role in the disease, or their association is unclear. For example, the R74W and D1270N mutations, long thought to play a causative role in CF, have been found in asymptomatic individuals and are now believed to be benign polymorphisms (*7*).

Indeed, it was to improve clarity of testing results that the ACOG removed two of the 25 mutations recommended in its initial 2001 study. Using a much larger data pool, the 2004 study determined that CF patients with the I148T mutation also have a second mutation, 3199del6, which appears from several lines of evidence to be the

Table 1: AGOG/ACMG 23 Recommended Mutation Panel

ΔF508	ΔI507	R117H	1717-1G>A
R553X	621+1G>T	R334W	2789+5G>A
R1162X	G85E	3849+10kbC>T	W1282X
2184delA	1898+1G>A	G551D	A455E
3120+1G>A	G542X	R347P	711+1G>T
3659delC	N1303K	R560T	

Table 2: Residual Risks to Fetus with ACOG/ACMG 23 Test			Estimated Residual Risk to Fetus	
Ethnicity	Detection Rate	Estimated Carrier Rate (5)	No Test	Both Partners Negative
Ashkenazi Jewish	94%	1:29	1:3,300	1:934,000
Non-Hispanic Caucasian	89%	1:25	1:3,300	1:207,000
Hispanic American	69%	1:46	1:8,464	1:125,000
African American	69%	1:65	1:16,900	1:176,000
Asian American	49%	1:90	1:32,400	1:125,000

mutation truly responsible for causing disease (*2*). Therefore, testing for I148T does not add value for purposes of disease prediction. When deciding which test to use for carrier screening, it is important to consider that a couple could decide not to pursue having children or continue a pregnancy based on a positive result for a low-frequency or poorly characterized mutation, such as I148T, that has no demonstrated link to the disease and is, in fact, a benign polymorphism.

In choosing the 23 mutations that constitute its recommended panel, ACOG/ ACMG stipulated that the mutation must be present at a frequency of at least 0.1% in the U.S. population (*2*). This is an extremely low frequency, and one at which detection of mutation recurrence begins to blur with background noise (*8*). Therefore rarer mutations are not likely to be consistently documented, let alone correlated significantly with disease. In addition, positive control standards are not available for almost all mutations outside the 23 in the ACOG/ AMCG panel.

Recommendations for Screening and Counseling Procedures

Cystic fibrosis is a complicated disease, with a broad range of mild to severe phenotypes, and one for which therapeutic options are expanding rapidly. The severity of disease can be affected by combinations of mutations in ways that are not entirely predictable based on current data. This range of clinical outcomes and lack of certainty must be conveyed to parents in order to ensure informed consent for CF carrier screening. Advanced expertise in human genetics is required for interpreting and reporting CF carrier screening results according to ACMG Standards and Guidelines, as well as for providing genetic counseling to parents.

Screening for genetic variance in the CFTR gene outside the recommended 23 mutation panel can cloud genetic counseling and parental decision making considerably. For example, negative results for additional variations can bestow a false sense of security, when the fact is that little about the role of these or other rare variants is known. On the other hand, positive results for these rare variations cannot be tied to specific phenotypic outcomes and therefore do not provide value toward informed and aware choices.

In summary, as diagnostic technologies become more sophisticated and genetic data becomes easier to obtain, it will be possible to gather more data on CF mutations. More data does not necessarily lead to a better result, however, if clinical relevance is poorly established. In the end, a high standard of patient care and experience is best fulfilled through use of the ACOG recommended 23-mutation panel for cystic fibrosis carrier screening.

[1] Mutations appearing at 0.1% frequency in at least one of the four ethnic groups or at 0.1% frequency when data from all four groups is pooled and averaged.

Article Provided By Nanogen, Inc.

For more information concerning Nanogen, call 1-877-626-6436, or visit the company's Web site at www.nanogen.com.

References:

1. Grody WW, Cutting GR, Klinger KW, *et al*. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. *Genet Med*. 2001; 3(2):149-54.
2. Watson MS, Cutting GR, Desnick RJ *et al,* Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genet Med.* 2004;6(5):387-91.
3. Cystic Fibrosis Mutation Database (http://www.genet.sickkids.on.ca/cftr/).
4. Genetic Testing for cystic fibrosis. NIH Consensus Statement 1997:15(4): 1-37.
5. The American College of Obstretics and Gynocology and American College of Medical Genetics (2001) Preconception and Prenatal Carrier Screening for Cystic Fibrosis. Clinical and Laboratory Guidelines.
6. Paladino T. Cystic fibrosis: status on genetic testing. Nanogen Presentation. 2006.
7. Claustres M, Altieri J-P, Guittard C, *et. al.* Are p.I148T, p.R74W and p.D127ON cystic fibrosis causing mutations? BMN Medical Genetics. 2004 5:19.
8. Tsongalis, GJ, Belloni, DR, Grody, WW. Cystic fibro sis mutation analysis: how many is enough? (Letter to Editor) Genetics in Medicine 6 (5):456-458.