



Cystic Fibrosis Carrier Screening and Diagnosis

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Cystic Fibrosis (CF) is one of the most common autosomal recessive diseases in Caucasians of Northern European descent and the Ashkenazi Jewish population. In these populations, the carrier frequency and disease incidence are about 1/25 to 1/29 and 1/2500 to 1/3300, respectively. The disease incidence in other ethnic groups is significantly less frequent. Estimated pre-test and post-test carrier risk with regard to ethnic group is provided in Table 1. For couples in whom both individuals are CF carriers, the risk for an affected child is 1 in 4.

Cystic Fibrosis is a multi-organ disease with predominantly respiratory and pancreatic manifestations. Clinical presentations of CF are vastly heterogeneous, ranging from mild to moderate to severe symptoms and poor genotype/phenotype correlation. Other manifestations include intestinal malabsorption, meconium ileus, chronic intestinal obstruction, chronic sinusitis, diabetes mellitus, liver disease, pancreatitis, and male infertility.

In 1989 the CF gene, cystic fibrosis transmembrane conductance regulator (*CFTR*), was cloned and its gene product identified. The same year, the phenylalanine deletion at residue 508 of the *CFTR* protein was discovered ($\Delta F508$). This mutation is responsible for approximately 70% of CF alleles in Caucasians of Northern European descent, but for only 30% of mutations in individuals of Ashkenazi Jewish descent. To date, more than 1000 disease-associated mutations in the *CFTR* gene have been identified.

The *CFTR* protein is a cAMP-regulated chloride ion channel with impaired function in individuals with CF. Consequently, an abnormality in chloride ion transport across cell membranes results in an accumulation of viscous secretions in the pancreas and lungs. The classic clinical diagnosis is made by demonstration of an elevation in sweat chloride.

Recently, the American College of Medical Genetics (ACMG) and the American College of Obstetrics and Gynecology (ACOG) recommended that preconception CF carrier screening be offered to non-Jewish Caucasian and Ashkenazi Jewish couples, and made available to couples of other ethnic and racial groups. The recommendation asserts the use of a 25 mutation pan-ethnic panel that includes all CF-causing mutations with an allele frequency of $\geq 0.1\%$ in the general U.S. population.

Accordingly, PAML is now offering CF mutation screening consistent with the ACMG and ACOG recommended pan-ethnic panel and reflex testing for benign variants I506V, I507V, and F508C. In the presence of R117H, a reflex test for the 5T polymorphism in intron 8 (IVS-8) will also be performed. The list of mutations detected is presented in Table 2.

In addition to CF mutation testing, PAML offers the opportunity of expert telephone consultation with a board-certified medical geneticist who will answer questions, provide guidance, and discuss pertinent issues in genetic counseling. Should you have any questions about CF testing, please call Bassem A. Bejjani, M.D. at (509) 474-6878.

Methodology

Genomic DNA is recovered from EDTA whole blood specimens. Target DNA is amplified by polymerase chain reaction (PCR) and probed for individual mutations with fluorophore-labeled probes by oligonucleotide ligation assay (OLA). OLA products are separated by capillary electrophoresis and detected by fluorescence.

Quick Facts

- ▶ Cystic Fibrosis is one of the most common autosomal recessive syndromes in Caucasian populations.
- ▶ The carrier frequency is as high as 1 in 25 in Caucasians of Northern European descent and the Ashkenazi Jewish population.
- ▶ The risk of having an affected child is 1 in 4 if both individuals of a couple are CF carriers.
- ▶ ACMG and ACOG jointly recommend that CF carrier screening be offered to all couples anticipating a pregnancy or seeking prenatal care.

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Continued

TABLE 1

Estimated Carrier Risk

Ethnic group	Detection rate	Estimated Carrier Risk	
		Before testing	After negative test
Ashkenazi Jewish	97%	1 in 29	~1 in 930
N. European Caucasian	80%	1 in 29	~1 in 140
African American	69%	1 in 65	~1 in 207
Hispanic American ^a	57%	1 in 46	~1 in 105
Asian American	b	1 in 90	b

^a This is a pool set of data and requires additional information to accurately predict risk for specific Hispanic populations.

^b No data available.

Note: Residual carrier risk after a negative test is modified by the presence of a positive family history of CF (i.e., having a first, second, or third degree relative affected with CF) and/or by admixture of various ethnic groups. For these specific situations, accurate risk assessment requires genetic counseling and standard Bayesian analysis. Data from Laboratory Standards and Guidelines for Population-based Cystic Fibrosis Carrier Screening. Genetics in Medicine 2001; vol 3:149-154.

TABLE 2 Mutations Detected in PAML CF Carrier Screen

American College of Medical Genetics Recommended 25 Mutation Panel with Reflex Testing			Additional mutations tested
R553X	W1282X	2789 + 5G → A	S549N
G551D	R334W	1898 + 1G → A	S549R
ΔI507	1078delT	621 + 1G → T	V520F
ΔF508	3849 + 10kbC → T	711 + 1G → T	3876delA
1717-1G → A	R1162X	G85E	R347H
G542X	N1303K	<i>Reflex:</i>	3905insT
R560T	3659delC	1506V	394delTT
3120 + 1G → A	A455E	1507V	F508C
R347P	R117H	IVS-8 5T	
I148T	2184delA		

Test Information

DESCRIPTION **CYSTIC FIBROSIS SCREEN**

METHOD PCR and OLA

ORDER CODE CFSCR

CPT CODE 83891, 83894, 83896 × 33, 83901, 83912

NOTE **This test must be ordered on a paper requisition that accompanies the specimen. It cannot be ordered using the PAML computer system.**

SPECIMEN 3-5 mL EDTA, sodium citrate, or ACD whole blood (lavender, blue, or yellow top tube).
Submit original and unopened tube only.

COMMENTS *Minimum amount:* 1 mL

Unacceptable conditions: Serum, heparinized whole blood, frozen whole blood, severely hemolyzed specimens, specimens in leaking containers or over 5 days old, specimens not received in the original collection tubes.

Stability: 72 hours at room temperature, 5 days refrigerated.

SCHEDULE Weekly

TURNAROUND 2 weeks

RANGES Cystic Fibrosis Carrier Screening: Negative for the mutations analyzed
Interpretation
Comments

Provided for the clients of

PATHOLOGY ASSOCIATES MEDICAL LABORATORIES
PACLAB NETWORK LABORATORIES
TRI-CITIES LABORATORY
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