



Excellence in Pathology and Laboratory Services

## Cystic Fibrosis Carrier Screening and Diagnostics

**Test Update**  
September/2005

### Overview

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 (1). 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.

Table 1. Estimated Carrier Risk\*

Ethnic group	Detection rate	Before testing	After negative test
Ashkenazi Jewish	97%	1 in 25	~1 in 800
European Caucasian	90%	1 in 25	~1 in 240
African American	72%	1 in 65	~1 in 229
Hispanic Americana **	57%	1 in 46	~1 in 108
Asian American	***	1 in 90	<1 in 90
Mixed Ethnicity	***		
Other	**		

\*Estimated carrier risks are for individuals with a negative family history of CF.

\*\*This is a pooled set of data and requires additional information to predict risk accurately for specific Hispanic populations.

\*\*\*No data available for Asian Americans or other ethnic populations.

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 (2). Other manifestations include intestinal malabsorption, meconium ileus, chronic intestinal obstruction, chronic sinusitis, diabetes mellitus, liver disease, pancreatitis, and male infertility (3, 4).

Analysis of selected mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, located at 7q31(2), allows direct DNA diagnosis for the purpose of carrier risk revision, confirmation of diagnosis and prenatal diagnosis.

To date, more than 1000 disease-associated mutations in the CFTR gene have been identified (5).

In 2001 the American College of Medical Genetic (ACMG) and the American College of Obstetrics and Gynecology (ACOG) finalized a description of a mutation panel that is now recommended for general population screening, and not just those with a personal or family history of carrying the CF gene (5). PathGroup Labs Cystic Fibrosis CF40 panel uses TM Biosciences Tag-It(TM) CF technology that simultaneously screens for the 25 CFTR gene mutations and 4 variants (polymorphisms) recommended by ACMG and ACOG, plus 15 of the world's most common and

North American-prevalent mutations as shown in Table 2. This assay incorporates multiplex PCR and multiplex Allele Specific Primer Extension (ASPE) with the universal Tag sorting on the Luminex® 100 xMAP™ platform for CFTR mutation detection. This is the first human disease genotyping test to be cleared by the U.S. Food and Drug Administration (FDA) as an in vitro device (IVD) for diagnostic detection and identifying of

mutations and variants in the CFTR gene in human blood specimens in order to determine CF carrier status in adults, as an aid in newborn screening, and in confirmatory diagnostic testing in newborns and children. Performance testing has established that the Tag-It(TM) CF Kit operates with 100% accuracy and greater than 99.9% reproducibility and precision.

Table 2. **Mutations Detected in PathGroup Labs CF 40 Panel.**

ΔF508*	A455E*	3849+10KBC>T*	2183AA>G
ΔI507*	1717-1G>A*	W1282X*	2307insA
G542X*	R560T*	N1303K*	Y1092X
G85E*	R553X*	394delTT	M1101K
R117H*	G551D*	Y122X	S1255X
I148T*	1898+1G>A*	R347H	3876delA
621+1G>T*	2184delA*	V520F	3905insT
711+1G>T*	2789+5G>A*	A559T	5T/7T/9T
1078delT*	3120+1G>A*	S549N	F508C
R334W*	R1162X*	S549R (T>G)	I507V
R347P*	3659delC*	1898+5G>T	I506V

\* ACMG-recommended

**Variant: 5T/7T/9T, I506V, I507V, F508C**

## **Clinical Utility**

### **Carrier Study (CF40C)**

- Revision of carrier risk for an individual with a positive family history of CF
  - Revision of carrier risk for an individual whose partner has a positive family history of CF
  - Revision of a carrier risk for an individual with a negative family history who is planning a pregnancy.
- Note: A negative mutation analysis reduces carrier risk, but does not exclude the possibility that the patient is a carrier.*

### **Diagnostic Study (CF40D)**

- Diagnosis of CF in a symptomatic newborn
- Diagnosis of CF in a neonate with equal clinical findings
- Identification of familial mutation in an affected patient
- Identification of mutations in an infertile male with congenital bilateral absence of the vas deferens (CBAVD).

**Methodology:** TM Biosciences TagIT 40+4 mutation detection assay (PCR and Allele Specific Primer Extension)

**Specimen Collection:** 3-5 ml EDTA or ACD whole blood (lavender or yellow-top tube). Store and transport at room temperature. If delayed more than 72 hours, store and transport refrigerated. Do not freeze specimen.

**Interpretation of Results:** PathGroup Labs requires pre-analytic clinical information in order to interpret the test results. Specifically, the test indication (carrier study, diagnostic study as shown by the test code), the patient's ethnic background, and family history of CF should be detailed on the Molecular Genetics Requisition Form or on electronic order. It may be necessary to test an additional family member in order to interpret a negative result for a patient with a positive family history of this disease. Appropriate counseling should follow CF mutation analysis so the patient fully understands the residual risk associated with a negative result and the reproductive ramifications of a positive result.

PathGroup Lab offers genetic counseling through the Division of Medical Genetics, Vanderbilt University. For more information on genetic counseling please contact their division at: (615) 322-7601, or go to: [www.vanderbiltchildrens.com/medicalgenetics](http://www.vanderbiltchildrens.com/medicalgenetics)

### Ordering Information

Test Code	Test Name	Specimen Type, Requirements
CF40C	Cystic Fibrosis Carrier Study	3-5 mL EDTA, or ACD whole blood (lavender, or yellow top tube).
CF40D	Cystic Fibrosis Diagnostic Study	3-5 mL EDTA, or ACD whole blood (lavender, or yellow top tube).

All specimens are stable for 24 hours at room temperature, 5-7 days refrigerated.

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

**Reference Ranges:** Negative for the CFTR mutations analyzed

**Turnaround Time:** 3-5 days

### References

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- Leus J, Van Biervliet S, Robberecht E. Detection and follow up of exocrine pancreatic insufficiency in cystic fibrosis: a review. Eur J Pediatr 2000;159:563-8.
- Grody WW. Cystic fibrosis: Molecular diagnosis, population screening and public policy. Arch Pathol Lab Med 1999;123:1041-6.
- ACOG News Release - OB-GYNS Offering Large-Scale Cystic Fibrosis Screening. December 12, 2001