



Cystic Fibrosis *CFTR* Gene Deletion or Duplication

Test code: 16080X

Clinical Use

- Diagnose cystic fibrosis (CF)
- Diagnose atypical CF in individuals with congenital bilateral absence of the vas deferens (CBAVD) or other conditions associated with the CF transmembrane conductance regulator (*CFTR*) gene
- Assess the risk of having a child with CF

For use when clinically indicated after 1) standard mutation panel testing has demonstrated <2 *CFTR* mutations; or 2) a large *CFTR* deletion or duplication has been detected in a family member.

Clinical Background

CF is a common autosomal recessive disorder characterized by chronic obstructive pulmonary disease, pancreatic exocrine deficiency with malabsorption and malnutrition, and CBAVD leading to male infertility. Atypical CF often affects only 1 organ system.

CF is caused by mutations in the *CFTR* gene, located on the long arm of chromosome 7 (7q31.2). More than 1300 *CFTR* mutations have been identified to date.¹ Although most affect only 1 or a few nucleotides, more than 25 large deletions or duplications have been described. Because standard mutation panels and sequencing assays do not detect such rearrangements, their actual frequency may be grossly underestimated.

Routine carrier screening detects 23 of the most commonly identified *CFTR* mutations.² The sensitivity of the screening panel for identifying mutant alleles is highest for Ashkenazi Jewish Caucasians (97%) and can be much lower for other populations: 90% for non-Hispanic Caucasians, 69% for African Americans, and 57% for Hispanic Americans; the sensitivity among Asian Americans is unknown.³ Thus, further testing is sometimes needed to identify both mutations in individuals with classic or atypical CF. Family members of CF patients whose mutations are not known may also require additional testing.

Extensive sequence analysis (eg, CF Complete™ Rare Mutation Analysis) can markedly increase the sensitivity of *CFTR* mutation screening, but this approach will not identify large duplications or deletions. The Cystic Fibrosis

CFTR Gene Deletion or Duplication assay detects deletions and duplications within the promotor region and all 27 exons of the *CFTR* gene. Recent studies suggest that such rearrangements may account for 16% to 24% of mutant *CFTR* alleles not identified after extensive sequencing.^{4,7} Because of the shorter turnaround time of the *CFTR* deletion/duplication test, clinicians may prefer to request it first and order extensive sequencing only if the result is negative.

Individuals Suitable for Testing

- Individuals with symptoms of classic or atypical CF who have <2 *CFTR* mutations detected with standard mutation screening
- Individuals with a family history of a large deletion or duplication in the *CFTR* gene
- Family members of individuals with CF whose mutations are unknown

Specimen Requirements

5 mL room-temperature whole blood in EDTA (lavender-top) tube; 3 mL minimum. For other sample types (blood, tissue, amniotic fluid), please contact the laboratory.

Please provide indication for testing, patient ethnicity, family history, and clinical information (eg, age, ethnicity, sweat chloride values, immunoreactive trypsinogen results, other *CFTR* mutations detected).

Method

- Semi-quantitative fluorescent polymerase chain reaction (SQF-PCR)
 - Amplification of *CFTR* promotor region and all exons (1-27) in a single multiplex SQF-PCR
 - Automated (capillary electrophoresis) separation of fragments and analysis of data
 - *CFTR* exon mutations detected as an approximate 50% signal decrease for deleted exon(s), and a 30% to 50% signal increase for duplicated exon(s)
- Alias: CFTR deletion/duplication
- CPT codes*: 83891; 83901 (x2); 83894 (x2); 83912

Reference Range

Not detected

Interpretive Information

The following information will help with interpretation of test results. Additional assistance is available from our Genetic Counselors by calling 1-866-GENE-INFO (1-866-436-3463).

Diagnosis: In the presence of positive clinical findings or family history, detection of 2 *known CFTR* mutations—or 1 in addition to a previously identified mutation—is consistent with a diagnosis of CF. The absence of clinical correlation data for *novel* mutations precludes a firm interpretation of their clinical effect. However, large deletions and duplications would be expected to impair CFTR protein function and thereby lead to disease in the presence of a second mutant allele. Negative results do not rule out the presence of an undetected *CFTR* mutation and therefore do not exclude a diagnosis of CF. This assay will not detect translocations or mutations outside the regions tested and may not detect small mutations such as single-nucleotide substitutions. Testing with extensive *CFTR* sequencing may detect rare mutations not identified by this assay.

Carrier Screening: The presence of a single *known* CF mutation in an asymptomatic individual identifies that person as a carrier. The relevance of a single *novel* mutation in this setting is not known. However, as described above, large deletions or duplications would be expected to negatively affect CFTR function and lead to disease in the presence of a

second mutant allele. Negative results do not eliminate the risk of being a carrier. Testing with extensive *CFTR* sequencing may detect rare mutations not identified by this assay.

References

1. Cystic Fibrosis Mutation Database. Cystic Fibrosis Consortium Web site. Available at <http://www.genet.sickkids.on.ca/cftr>. Accessed May 12, 2005.
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3. Richards CS, Bradley LA, Amos J, et al. Standards and guidelines for *CFTR* mutation testing. *Genet Med*. 2002;4:379-391.
4. Niel F, Martin J, Dastot-Le Moal F, et al. Rapid detection of *CFTR* gene rearrangements impacts on genetic counselling in cystic fibrosis. *J Med Genet*. 2004;41:e118.
5. Audrezet MP, Chen JM, Ragueneas O, et al. Genomic rearrangements in the *CFTR* gene: extensive allelic heterogeneity and diverse mutational mechanisms. *Hum Mutat*. 2004;23:343-357.
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7. Bombieri C, Bonizzato A, Castellani C, et al. Frequency of large *CFTR* gene rearrangements in Italian CF patients. *Eur J Hum Genet*. 2005;13:687-689.

*The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payor being billed.

This test was developed and its performance characteristics determined by Quest Diagnostics Nichols Institute. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test. Polymerase chain reaction (PCR) is performed pursuant to a license agreement with Roche Molecular Systems Inc.

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TS1684-HS 08/2005