



# CYSTIC FIBROSIS (CF) SCREENING

## Parental Genetic Screening

### Indications

#### CF 48

Carrier (parental) screening when planning pregnancy

All white of European and Ashkenazi Jewish descent (offer)

All other couples (make available)

Embryonic Screening (amniotic fluid)

#### CF 100

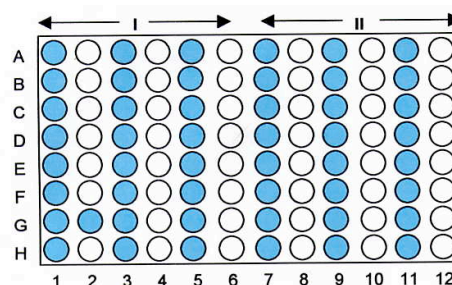
Carrier (Parental) screening when planning pregnancy

Spouse of known CF carrier

Normal parents with affected (CF) child

Normal patient **or** spouse who has affected (CF) sibling

Males with CBAVD **and** their wives



Example of a plate appearance for CF-48 test of a DF508 positive heterozygous specimen

### Scientific background

The cause for cystic fibrosis, identified in 1989, is a mutated chloride channel gene also identified as cystic fibrosis trans-membrane conductance regulator (CFTR). The gene, located on chromosome 7, is 250kb in size (6500 bp mRNA), and its encoded protein is 1480 amino acids - ~170kd in size (1,3). This molecule selectively allows chloride ions through the (epithelial) cell membrane. Chloride ion transport is an important biochemical function as it is involved in maintenance of trans-membrane potential and thus affects membrane functions, which are sensitive to this electric milieu. Moreover, chloride channels are involved in controlling salt concentrations next to the (epithelial cell) membrane surface, which in turn affect the water accumulation at the affected surfaces and the rheologic (flow-related) parameters of secretions (rendering them more viscous) in various exocrine glands particularly of sweat and mucus and in the pancreas. These are major parameters in the normal physiology of lungs and intestine and, therefore, when a dysfunctional chloride channel protein exists, pathophysiology of these organs ensues.

### Clinical background

CF is the most common lethal genetic defect in white populations, characterized by mal-

absorption in infancy and childhood, chronic pulmonary disease (the major cause for morbidity and mortality), exocrine pancreatic insufficiency, abundance of cases with sinusitis and nasal polyps, elevated sweat electrolyte level and typically, male infertility. Life expectancy for CF affected patients today is ~29 and 32 years for males and females respectively with intense, costly care. There is as yet no cure to the disease, and all current treatments are symptom-relieving, functional deficiency supplementations, etc. that address the specific symptoms and organ dysfunctions. Genetic screening of couples with or without a family history of CF will allow more accurate genetic counseling as well as more informed reproductive choices. CF is inherited as an autosomal recessive genetic disease. Hence there is a 25% chance for two carriers to have an affected child. If only one of the parents is a carrier, the offspring have a 50% probability of being a carrier. While the general frequency of the disease is ~1:2500 births, the frequency of being a carrier is related to ethnic/racial origin, being highest (1:25) in European Caucasians and Ashkenazi Jews. Hispanic Americans, African Americans and Asian Americans have a 1:46, 1:65 and 1:90 chance respectively of carrying the mutation (2, 4). 70% of all Caucasian carriers have a deletion of the codon for the amino acid phenylalanine at position 508

(ΔF508), which has also been associated with male infertility due to congenital bilateral absence of vas deferens (CBAVD), and hence the significance for CF testing for male infertility. However, there are more than 1,000 mutations in this gene identified to date (that have clinical significance). In general, screening for genetic diseases is recommended when the prevalence of being a carrier is >1%, which includes most ethnicities for CF. A more intensive CF screen must be offered for subjects at a higher risk. We offer a screen for the 48 most common mutations (CF-48), which has an 85-90% chance of detecting all carriers of CF. These cover all the *standard mutation panel's* 25 mutations recommended by the ACOG/ACMG guidelines for CF screening. We also offer a screen of 100 mutations (CF-100), which includes all of the above mutations and has a ~92% detection probability for the higher risk subjects.

#### Test methodology

CF-48 Test is based on gene region-specific DNA amplification (multiplex polymerase chain reaction) (PCR) followed by allele-specific Oligonucleotide Ligation Assay (OLA) using colorimetric monitoring with labeled hybridization probes. For each mutation tested, the PCR/OLA method could distinguish between wild type homozygous, carrier (heterozygous), as well as afflicted patient, homozygous for the mutation.

CF-100 analysis is performed by gene region-specific DNA amplification (PCR) followed by the primer oligonucleotide base extension (PROBE) of the mutation target. The resulting diagnostic products are then measured by mass spectrometry (MS) that has resolution significantly higher than DNA sequencing.

#### Units and ranges

Results will identify the mutation(s)/deletion(s) site in the gene - expressed as the respective amino acid location in the protein or the nucleotide position and identification in the gene, as the case may be. It will also state whether proband is heterozygous or homozygous (e.g. in CBAVD where proband is affected) for those mutations.

#### Sample requirement

One purple-top vacutainer (10 ml) EDTA whole blood. Ship at ambient temperature before 5 p.m.

on the same day by 'FedEx Priority Overnight' to arrive at Repromedix before 10:30 a.m. the following day.

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12. Callanan NP, Chevront B, Sorenson JR. (1999) CF carrier testing in a high risk population: anxiety, risk perceptions, and reproductive plans of carrier by "non-carrier" couples. *Genet Med 1 (7)*:323-327.



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