*Before, Between & Beyond Pregnancy*
**The National Preconception Curriculum and Resources Guide for Clinicians**

# Guidance for Preconception Cystic Fibrosis Carrier Screening

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Summary of the Genetics of Cystic Fibrosis

*Dequeker E, Stuhrmann M, Morris MA, Casals T, Castellani C, Claustres M, Cuppens H, des Georges M, Ferec C, Macek M, Pignatti P, Scheffer H, Schwartz M, Wit M, Schwarz M, Girodon E. Best practice guidelines for molecular genetic diagnosis of cystic fibrosis and CFTR-related disorders – Updated European recommendations. European Journal of Medical Genetics 2009;17:51-65.*

Cystic fibrosis transmembrane conductance regulator (CFTR) gene studies are some of the most frequently performed genetic analyses throughout the world. More than 1500 sequence variations have been reported in the CFTR gene, often with geographic or ethnic variations in frequency. Mutations have been associated with both classic cystic fibrosis and CFTR-related disorders, including congenital bilateral absence of the vas deferens (CBAVD), disseminated bronchitis, chronic pancreatitis or chronic rhinosinusitus.

A good knowledge of CFTR diseases and their molecular pathology is required when choosing testing methodologies and interpreting results. Molecular testing for CFTR mutations relies mainly on direct gene analysis. Methods include targeted mutation analysis, or testing DNA samples for the presence or absence of specific mutations, and scanning methods, screening samples for any deviation from the standard sequence. Targeted mutation analysis is most commonly used to routine carrier screening. Scanning methods are useful in the detection of large unknown CFTR rearrangements, which can escape detection using conventional amplification assays, and have been shown to occur in up to 2% of patients with CF and 1% of patients with CBAVD. Even with all available testing methods, approximately 1-5% of mutations cannot be detected in patients with classic CF and even more in patients with atypical presentations.

Laboratories performing routine carrier screening usually optimize their panels for American and/or Western European populations, resulting in lower test sensitivities in other populations. It is important to be aware of the actual or estimated mutation

detection rate in a given patient population and determine when additional testing for rare or additional testing should be sought. Therefore, the quality of the final result depends not only on the laboratory procedures, but also on the referral information provided to ensure the appropriate testing is performed. Appropriate pre- and post-test counseling for patients is also essential. When a negative result is reported, the residual risk of carrier status, calculated using Bayesian analysis, should be reported to the patient.

When a homozygous affected person is identified, assignment of correct parental alleles is necessary for possible prenatal diagnosis in future pregnancies and for carrier testing in at-risk relatives. As de novo mutations are exceptionally rare, if mutations are not found in both parents, the possibilities of non-paternity and a sample mix-up should be considered.

Fetal bowel abnormalities including hyperechogenicity and/or loop dilation have been associated with an increased risk for cystic fibrosis. Diagnostic investigations should include evaluation for the most frequent CFTR mutations by parental carrier and/or prenatal diagnosis, fetal karyotyping and screening for viral infections such as cytomegalovirus (CMV).

CFTR mutations are associated with a broad range of phenotypes, mainly due to their varied effects on protein synthesis and function. Only mutations that cause cystic fibrosis should be considered for carrier testing and prenatal diagnosis. If a variant is detected, it is essential for laboratories to make clear whether a detected variant is predicted to cause CF, to have a severe or moderate affect, to be associated with CFTR-RD, or to be phenotypically normal. Reports should be issued in a standardized form, clearly intelligible to the non-specialist.

Common identified variants include 5T, I148T and R117H. The 5T allele, or (T)5 as it is known in the European literature, is a splicing variant of the intron 8 acceptor splice site. There are three common alleles at the polypyrimidine tract of the intron 8 acceptor splice site, named by the number of thymidines present: 5T, 7T and 9T. The lower the number of thymidines, the lower the efficiency of exon 9 splicing. The number of adjacent TG repeats can also affect the efficiency of splicing. Therefore, when the 5T variant is discovered, the TG repeat length should also be examined. The inheritance of a 5T variant and TG12 or TG13 in trans with a CF-causing mutation may result in a mild form of CF, thus requiring clinical evaluation and long term follow-up.

The I148T variant was originally thought to be a CF-causing mutation. Recent data have shown it is not CF-causing in itself and the variant is currently being removed from screening panels.

The R117H allele can be found in cis with the 5T and 7T variants. When inherited with a disease causing mutation, the combination of R117H and 5T has been associated with mild CF. Children who are compound heterozygotes for R117H/7T and a CF-causing mutation have shown no clinical symptoms.