

Cystic Fibrosis

Posted 11-29-04

Key Points

- Cystic fibrosis (CF) is caused by mutations in the *CFTR* gene and is inherited in autosomal recessive manner.
- Parents need help adjusting to the diagnosis of CF and accessing the best medical treatment available for their child.
- Among the non-Hispanic white population, molecular genetic testing using a panel of common mutations can identify 85-90% of disease-causing mutations in the *CFTR* gene.
- The diagnosis of CF in one child raises the possibility that the condition could be present in siblings.
- Molecular genetic testing to detect affected siblings may also identify sibs who are carriers, raising ethical concerns about testing minors.

Learning Objectives

Participants will be able to:

- Compare and contrast the use of molecular genetic testing and sweat chloride testing in establishing the diagnosis of CF;
- Explain why some individuals with CF may not have identifiable mutations in the *CFTR* gene;
- Describe the social and ethical issues associated with a new diagnosis of CF.

See [GeneReview: CFTR-Related Disorders](#).

Family History Issues

Cystic fibrosis can occur in the absence of family history of the disease. Cystic fibrosis is inherited in an autosomal recessive manner, meaning that both parents of an affected individual are usually carriers of a mutation in the *CFTR* gene. A *CFTR* mutation can be transmitted from generation to generation with no affected individuals in the family. However, if a carrier has a child with another carrier, there is a 25% chance that the child will be affected.

Red Flags



Symptoms suggestive of cystic fibrosis include **chronic sinopulmonary disease** (chronic cough and sputum production, chronic wheeze and air trapping, obstructive lung disease on lung function tests, persistent bacterial colonization, chronic chest radiograph abnormalities, digital clubbing) and **gastrointestinal/nutritional abnormalities** (malabsorption/pancreatic insufficiency, distal intestinal obstructive syndrome, rectal prolapse, recurrent pancreatitis, meconium ileus, chronic hepatobiliary disease, failure to thrive, hypoproteinemia, fat-soluble vitamin deficiencies). In the male of reproductive age, the lack of reproductive capacity, due to congenital bilateral absence of the vas deferens (CBAVD), may be the only presenting symptom.

In addition, many states have introduced newborn screening for CF, resulting in the detection of asymptomatic infants with CF.

Case 12. Failure to Thrive: Workup Results in Diagnosis of Cystic Fibrosis

Mr. and Mrs. M, a white couple, have two children, a four-year-old son and a three-month-old daughter. The three-month-old has had considerable difficulty gaining weight and has undergone a workup for failure to thrive, resulting in the diagnosis of cystic fibrosis by a sweat chloride test. Mr. and Mrs. M are very concerned about this diagnosis and its implications. There is no family history of CF. Their son gets frequent colds, but is otherwise in good health.

Clinical Care Issues

Adjusting to the diagnosis of a chronic disease. The diagnosis of CF in Mr. and Mrs. M's three-month-old child indicates that this child will have chronic health problems, with potential social, emotional, and financial burdens for the family. The family may need ample opportunities to ask questions and learn more about CF, over time, as they adjust to this new circumstance.

Possibility of CF in the older child. Their four-year-old son could also be affected. He has some clinical findings that are consistent with a mild presentation of the disease; however, these findings are also seen in many children without CF. Sometimes the diagnosis of an autosomal recessive condition in one child leads to the diagnosis of siblings. The four-year-old can be evaluated for CF by having a sweat chloride test and/or by molecular genetic testing. Either of the two following test results would be diagnostic for CF: two abnormally elevated sweat chloride values; or detection of the same two disease-causing mutations in the *CFTR* gene as identified in his affected sister or in his parents. While molecular genetic testing **may be more accurate**, it may have some **ethical implications**. If their son is not affected, his CF carrier status would be revealed through such testing.

Risk Assessment

Relevant risk factors. Cystic fibrosis is inherited in an autosomal recessive manner, and thus children of this couple have a 25% risk of being affected.

Role of family history and age of onset in assessing risk. Even though the risk of CF for a sibling of an affected individual is 25%, the chance that the four-year-old brother is affected is probably less than that, given that approximately 80% of individuals with CF are diagnosed by age two years. However, some individuals with milder forms of CF are not diagnosed until adulthood, including males whose only symptom of CF is CBAVD. Therefore, based on clinical presentation, the chance that the four-year-old has CF is less than 25% but is not negligible.

Genetic Counseling and Testing

Genetic counseling offers the family the opportunity to learn more about the genetics of CF and the implications of their daughter's diagnosis for other family members. Genetic counseling will include a discussion of genetic testing options and risks for other family members to be CF carriers.

Genetic testing options

More than 1000 mutations have been detected in the *CFTR* gene. However, most commercially available tests consist of a panel of 25 common mutations (recently reduced to 23 mutations; see [Watson et al 2004](#)), a test which detects approximately 85-90% of mutations in non-Hispanic whites

(see [GeneReview: Table 8](#)).

In an individual with a confirmed diagnosis of CF, it is possible that 0, 1, or 2 mutations will be detected by molecular genetic testing (see [GeneReview: Table 2](#)). If initial testing of a child affected with CF does not identify two mutations, an expanded panel of mutations (i.e., >23) may be used to detect more mutations; this approach may be particularly useful among ethnic minorities [[Heim et al 2001](#); [GeneReview: Table 1](#)]. *CFTR* gene sequencing is available through a few commercial labs. Although this can detect more mutations, it can be very expensive and involve a longer turnaround time. In the majority of cases, it is more practical to start with a panel with a high detection rate.

Should this family be offered molecular genetic testing?

Molecular genetic testing would typically be conducted in the three-month-old with CF for the following reasons:

- Test results may provide some information about the child's prognosis because some mutations are associated with a milder course.
- If both CF mutations are identified, molecular genetic testing could be used to determine whether siblings are also affected (for example, in this case, the older sibling who has shown some mild symptoms of CF).
- If both mutations are identified, the carrier status in other relatives could be clarified through molecular genetic testing.
- If both mutations are identified, prenatal diagnosis of subsequent pregnancies for Mr. and Mrs. M would be available.

What is the optimal testing strategy for this family?

Initial testing should be done on the three-month-old who has been diagnosed with CF to determine whether she has two identifiable *CFTR* mutations. Then, various approaches are possible for the four-year-old sibling. He can either be evaluated with a sweat chloride test or (if his sister has two identifiable mutations) by molecular genetic testing. If either of these tests is positive, he would be given the diagnosis of CF. Molecular genetic testing would also allow for the determination of the carrier status of this child.

If molecular testing reveals only one mutation in the three-month-old, then the four-year-old cannot be evaluated for CF using molecular genetic testing, and a sweat test should be used.

Although Mr. and Mrs. M are both likely obligate carriers of CF, they may also have molecular genetic testing to determine which mutation is segregating in each of their families. This would provide information to their relatives who may be considering carrier testing. If the specific *CFTR* mutation identified in the family is not one of the 23 common mutations included in the usual test panel, a relative's health care provider would need to ensure that the mutation identified in the family is included the panel used for carrier testing.

Interventions

Preventive care. Many strategies are used to manage the pulmonary and gastrointestinal complications associated with cystic fibrosis (see [GeneReview: Management](#)).

Other clinical management. Referral to a regional CF Center is recommended for individuals known to have CF or those in whom the diagnosis is being considered. A local CF clinical care center can be identified by contacting the [CF Foundation](#). Most patients followed at a CF Center are evaluated quarterly by a multidisciplinary team consisting of physicians, nurses, respiratory therapists, dietitians, social workers, and genetic counselors. Frequent monitoring and increased use of appropriate medications in the management of CF have resulted in improved outcomes [[Johnson et al 2003](#)].

Ethical/Legal/Social/Cultural Issues

The parents are coping with their daughter's diagnosis of CF. She will face chronic medical problems, and the current median age of survival in CF is about 32 years. This new diagnosis of CF in their daughter has also exposed a possible threat to their four-year-old son, who has displayed some symptoms of CF. If he were diagnosed with CF, he would also face chronic health problems and a diminished life expectancy, and, in addition, a 95% chance that he would be sterile. The social and ethical concerns include:

- Education of the couple
- Sharing information with relatives
- Providing the best care recommendations for the patient
- Identifying CF carrier status in a minor child
- Respecting reproductive choice

Education of the couple. Education involves having access to individuals and families dealing with CF as well as a variety of allied health professionals instrumental in treating individuals with cystic fibrosis. Many organizations and support groups are available to help families cope with the disease. Individuals who are in similar situations may best address the family's fears.

Sharing information with relatives. Other family members including Mr. and Mrs. M's siblings may be CF carriers. Mr. and Mrs. M should be encouraged by their physicians to provide medical information, including molecular genetic test results, to their relatives. Some relatives, especially those of reproductive age, may wish to have molecular genetic testing to determine if they are carriers and are at potential risk of having a child with CF. The CF carrier frequency and common *CFTR* mutations vary with ethnicity. Recurrence risk counseling for carrier relatives and their partners should be offered based on this information prior to testing. Of note, no current laws create legal obligations for either the family member or the physician to inform other family members about the hereditary nature of this condition, but there is a strong ethical claim to encourage family members to do so.

Best care. Referral to a regional CF Center is recommended for individuals known to have CF or those in whom the diagnosis is being considered, if possible, to ensure multidisciplinary care according to current practice standards. As the child matures, particular attention will need to be paid to the transition of care from a pediatrician to a provider of adult health care, because patients are now living well beyond the age of 18 years.

Identifying CF carrier status in a minor child. If Mr. and Mrs. M would like to pursue molecular genetic testing for CF in their older child, they should be counseled ahead of time that there are three possible results: the child could be determined to be affected with CF, unaffected, or a CF carrier.

There is an ethical concern regarding carrier testing in minors: such testing can reveal the child's future reproductive risks, potentially causing unnecessary worry or other psychosocial harm, and represents information would not be of value until later in the child's life [[ACMG/ASHG 1995](#)]. In general the identification of a carrier state in children is considered only if that information directly benefits the health of the child at the time of testing. If not, it is recommended that carrier identification should not be completed until the child becomes competent and capable of engaging in informed consent [[AAP 2001](#)].


However, in the present situation, genetic testing represents an effective method to determine whether the child has CF, assuming that two *CFTR* mutations have been identified in his sister. Prior counseling will allow the child's parents to prepare for the possibility that the test may identify the child as a CF carrier. One approach would be for the parents to use their discretion in determining at what age they will share the carrier information with their child. Alternatively, if the parents express concern about the psychosocial effects of identifying their child's carrier status, they could be offered two other options:

- Assessing the child's CF status via the sweat test instead of a molecular test, OR
- Reporting the molecular test results solely in terms of whether the child has CF, with carrier identification not reported

Respect for reproductive choice. Parents should be counseled regarding the 25% risk for future children to be affected with CF. If the parents decide to have more children, they will have the choice of undergoing prenatal diagnosis for CF in subsequent pregnancies.

Resources

- **Cystic Fibrosis Foundation**
6931 Arlington Road, 2nd Floor
Bethesda, MD 20814-5200
Phone: 800-FIGHTCF (800-344-4823); 301-951-4422
Fax: 301-951-6378
Email: info@cff.org
- **Cystic Fibrosis Trust**
11 London Road
Bromley
Kent BR1 1BY
England
Phone: 020 8464 7211
Fax: 020 8313 0472
After hours: 020 8464 0623
- **Medline Plus Health Information: Cystic Fibrosis**

- **Connecticut Children's Medical Center**
[Pediatric to Adult Care Transition for CF](#)
This site has a basic protocol for the transfer of patients from pediatric to adult care.
- **Institute of Child Health**
Great Ormond Street Hospital for Children NHS Trust
This site answers some basic questions about their transition program.
- American Society of Human Genetics and American College of Medical Genetics (1995) [Points to consider](#): ethical, legal, and psychosocial implications of genetic testing in children and adolescents
- American College of Medical Genetics (2000) [Statement](#) on genetic testing for cystic fibrosis
- **Cystic Fibrosis Medicine**
- **National Library of Medicine Genetics Home Reference**
[Cystic Fibrosis](#)
- **GeneTests Online Medical Genetics Information Resource**
- **GeneReviews, GeneTests Online Medical Genetics Information Resource**
- **GeneTests Resources for *CFTR*-Related Disorders** 

References

[CFTR-Related Disorders GeneReview, References](#)

American Academy of Pediatrics (2001) Policy statement: ethical issues with genetic testing in pediatrics. Committee on Bioethics. *Pediatrics* 107:1451-5 [[Medline](#)]

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