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Women's Health Care Physicians

COMMITTEE OPINION

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Committee on Genetics

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Update on Carrier Screening for Cystic Fibrosis

ABSTRACT: In 2001, the American College of Obstetricians and Gynecologists and the American College of Medical Genetics introduced guidelines for prenatal and preconception carrier screening for cystic fibrosis. The American College of Obstetricians and Gynecologists' Committee on Genetics has updated current guidelines for cystic fibrosis screening practices among obstetrician–gynecologists.

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive condition in the non-Hispanic white population. It is a progressive, multisystem disease that primarily affects the pulmonary, pancreatic, and gastrointestinal systems but does not affect intelligence. The current median survival is approximately 37 years, with respiratory failure as the most common cause of death. Approximately 15% of individuals with CF have a mild form of the disease with a median survival of 56 years (1). More than 95% of males with CF have primary infertility with obstructive azoospermia secondary to congenital bilateral absence of the vas deferens. Cystic fibrosis is caused by mutations in the *CF transmembrane regulator* (*CFTR*) gene, located on chromosome 7. Two copies of deleterious mutations in this gene cause CF. The disease incidence is 1 in 2,500 individuals in the non-Hispanic white population and considerably less in other ethnic groups.

Prenatal and preconception carrier screening for CF was introduced into routine obstetric practice in 2001 (2). The goal of CF carrier screening is to identify couples at risk of having a child with classic CF, which is defined by significant pulmonary disease and pancreatic insufficiency. Cystic fibrosis is more common among the non-Hispanic white population compared with other racial and ethnic populations; however, it is becoming increasingly difficult to assign a single ethnicity to affected individuals. It is reasonable, therefore, to offer CF carrier screening to all patients. The sensitivity of the screening test varies among different ethnic groups (Table 1), ranging from less than 50% in those of Asian ancestry to 94% in the Ashkenazi Jewish population (3). Therefore, screening is most efficacious in non-Hispanic white and Ashkenazi Jewish populations. Because testing is offered for only the most common mutations, a negative screen-

Table 1. Cystic Fibrosis Detection and Carrier Rates Before and After Testing

Racial or Ethnic Group	Detection Rate* (%)	Carrier Risk Before Testing	Approximate Carrier Risk After Negative Test Result†
Ashkenazi Jewish	94	1/24	1/380
Non-Hispanic white	88	1/25	1/200
Hispanic white	72	1/58	1/200
African American	64	1/61	1/170
Asian American	49	1/94	1/180

*Detection rate data based on use of a 23-mutation panel.

†Bayesian statistics used to calculate approximate carrier risk after a negative test result.

Modified from the American College of Medical Genetics. Technical Standards and Guidelines for CFTR Mutation Testing, 2006 Edition. Available at: http://www.acmg.net/Pages/ACMG_Activities/stds-2002/cf.htm. Retrieved December 16, 2010.

ing test result reduces, but does not eliminate, the chance of being a CF carrier and having an affected offspring. Therefore, if a patient is screened for CF and has a negative test result, she still has a residual risk of being a carrier. The most common CF carrier frequencies as well as the rates of residual carrier risk after a negative test result are listed by racial and ethnic group in Table 1.

Screening Considerations for Cystic Fibrosis

Preconception carrier screening allows couples to consider the most complete range of reproductive options. Knowledge of the risk of having an affected child may influence a couple's decision to conceive or to consider preimplantation genetic diagnosis, prenatal genetic testing, or the use of donor gametes. Generally, it is more cost effective and practical to perform initial carrier screening for the patient only. If the patient is a CF carrier, then her partner should be tested. During pregnancy, concurrent screening of the patient and her partner is suggested if there are time constraints for decisions regarding prenatal diagnostic evaluation. Given that CF screening has been a routine part of reproductive care for women since 2001, it is prudent to determine if the patient has been previously screened before ordering CF screening that may be redundant. If a patient has been screened previously, CF screening results should be documented but the test should not be repeated. The following are various carrier screening scenarios with associated management guidelines:

- *A woman is a carrier of a CF mutation and her partner is unavailable for testing or paternity is unknown.* Genetic counseling to review the risk of having an affected child and prenatal testing options and limitations may be helpful.
- *Prenatal diagnosis is being performed for other indications and CF carrier status is unknown.* Cystic fibrosis screening can be performed concurrently on the patient and partner. Chorionic villi or amniocytes may be maintained in culture by the diagnostic laboratory until CF screening results are available for the patient or couple. If both partners are carriers, the sample can then be tested for CF.
- *Both partners are CF carriers.* Genetic counseling is recommended to review prenatal testing and reproductive options. Prenatal diagnosis should be offered for the couple's known specific mutations.
- *Both partners are unaffected but one or both has a family history of CF.* Genetic counseling and medical record review should be performed to identify if *CFTR* mutation analysis in the affected family member is available.
- *A woman's reproductive partner has CF or apparently isolated congenital bilateral absence of the vas deferens.* The couple should be referred to a genetics professional for mutation analysis and consultation.
- *An individual has two CF mutations but has not previously received a diagnosis of CF.* These individuals usually have a mild form of the disease and should be referred to a specialist for further evaluation. Genetic counseling is recommended.

CFTR Mutation Panels

To date, more than 1,700 mutations have been identified for CF (4). The initial American College of Medical Genetics Cystic Fibrosis Carrier Screening Working Group (5) recommended that laboratories use a pan-ethnic panel of 25 mutations that were present in at least 0.1% of patients with classic CF. Current guidelines, revised by the American College of Medical Genetics in 2004, use a 23-mutation panel and were developed after assessing the initial experiences upon implementation of CF screening into clinical practice (6). Cystic fibrosis screening also may identify the 5T/7T/9T variants in the CFTR gene, which vary between individuals. Genetic counseling is important to discern whether the combination of mutations and variants would cause classic or atypical CF.

Complete analysis of the *CFTR* gene by DNA sequencing is not appropriate for routine carrier screening because it may yield results that can be difficult to interpret. This type of testing is generally reserved for patients with CF, patients with a family history of CF, males with congenital bilateral absence of the vas deferens, or newborns with a positive newborn screening result when mutation testing, using the standard 23-mutation panel, has a negative result. Because carrier screening detects most mutations, sequence analysis should only be considered after discussion with a genetics professional to determine if it will be of value to the evaluation after standard screening has been performed.

The decision to have CF carrier screening should be reached by informed choice. Patients should receive information about CF and its inheritance pattern. (Patient education brochures are available from the American College of Obstetricians and Gynecologists at sales.acog.org, and a sample patient script on CF is included in this document [see Box 1, "Information on Cystic Fibrosis to Share With Your Patients"]). It is important for patients and their partners to recognize the sensitivity and limitations of testing as well as their reproductive options.

All states include CF screening as part of their newborn screening panel. However, newborn screening panels that include CF screening do not replace maternal carrier screening. Because these screening programs generally identify affected newborns, a negative test result in an unaffected newborn provides no information regarding the carrier status of the parents. Thus, it is important that CF screening continues to be offered to women of reproductive age.

Box 1. Information on Cystic Fibrosis to Share With Your Patients

Cystic fibrosis (CF) is a genetic disorder that causes breathing and digestive problems. Intelligence is not affected by CF. Individuals with CF have a current life expectancy of approximately 37 years, and the cause of death usually is lung damage. Approximately 15% of individuals with CF have a mild form of the disease and live an average of 56 years. Common symptoms of CF include coughing, wheezing, loose stools, abdominal pain, failure to thrive, and, in men, infertility. Treatment involves medication to aid digestion, proper nutrition, and lung therapy.

Cystic fibrosis is an inherited condition that is caused by mutations in the *CFTR* gene. When a patient and her partner are both carriers of a mutation in the *CFTR* gene, they have a 1 in 4 chance of having a child with CF. To date, more than 1,700 mutations have been identified in the gene for CF. Screening for the 23 most common mutations is available and can greatly reduce a couple's risk of having a child with CF. The risk of being a carrier depends on an individual's race and ethnicity and family history. Cystic fibrosis is most common in non-Hispanic white individuals and people of Ashkenazi Jewish ancestry. A genetics specialist can help couples with a risk of having a child with CF by explaining and providing information about their reproductive options.

Health Considerations for Women With Cystic Fibrosis

Given the increasing longevity of affected patients, women with CF have reasonable fertility and often can become pregnant without medical assistance. Therefore, it is recommended that women with CF receive guidance regarding adequate contraception as well as preconception consultation. Affected women also should be informed that their offspring will be obligate carriers and that their partners should be tested to determine their carrier risk. If a woman with CF wants to become pregnant, a multidisciplinary team should be considered to manage issues regarding pulmonary function, weight gain, infections, and the increased risks of diabetes and preterm delivery.

Recommendations

Based on the preceding information, the Committee on Genetics provides the following guidelines:

- It is important that CF screening continues to be offered to women of reproductive age. It is becoming increasingly difficult to assign a single ethnicity to individuals. It is reasonable, therefore, to offer CF carrier screening to all patients. Screening is most efficacious in the non-Hispanic white and Ashkenazi Jewish populations.
- It is prudent to determine if the patient has been previously screened before ordering CF screening that may be redundant. If a patient has been screened previously, CF screening results should be documented but the test should not be repeated.
- Complete analysis of the *CFTR* gene by DNA sequencing is not appropriate for routine carrier screening.
- Newborn screening panels that include CF screening do not replace maternal carrier screening.
- If a woman with CF wants to become pregnant, a multidisciplinary team should be considered to manage issues regarding pulmonary function, weight gain, infections, and the increased risks of diabetes and preterm delivery.
- For couples in which both partners are carriers, genetic counseling is recommended to review prenatal testing and reproductive options.
- For couples in which both partners are unaffected but one or both has a family history of CF, genetic counseling and medical record review should be performed to identify if *CFTR* mutation analysis in the affected family member is available.
- If a woman's reproductive partner has CF or apparently isolated congenital bilateral absence of the vas deferens, the couple should be referred to a genetics professional for mutation analysis and consultation.

Resources

The resources listed are for information purposes only. Referral to these resources and web sites does not imply the endorsement of the American College of Obstetricians and Gynecologists. Further, the American College of Obstetricians and Gynecologists does not endorse any commercial products that may be advertised or available from these organizations or on these web sites. This list is not meant to be comprehensive. The exclusion of a source or web site does not reflect the quality of that source or web site. Please note that web sites and URLs are subject to change without notice.

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