Cystic fibrosis screening and diagnosis

Cystic fibrosis (CF) is the most common inherited disease that is fatal among Caucasian people in the United States. The incidence is estimated to be 1/3,000 live Caucasian births and approximately 1/29 Caucasians in the United States carry a single copy of the abnormal CF gene or are carriers. These rates are lower in non-Caucasians. Carriers are healthy individuals, usually unaware of their status unless they have an affected relative or undergo genetic testing. When one parent is a CF carrier, 50% of their offspring will also be carriers. Couples, in whom both partners carry a CF mutation, have a 25% chance of having an affected child with each pregnancy and a 66.6% chance that unaffected children will be carriers.

The gene that causes CF is located on chromosome 7 and directs the synthesis of cystic fibrosis transmembrane conductance regulator (CFTR). CFTR is a cAMP-regulated chloride channel in the apical membrane of epithelial cells. More than 1,000 different disease-causing mutations have been identified and are classified as severe or mild. Compounding the problem is the same CFTR genotypes may show variable expression in different patients, making it difficult to predict the phenotype. The most common mutation, seen in 70% of cases in Caucasians of northern European descent, is a 3-base pair deletion resulting in the loss of amino acid 508 (ΔF508del).

Diagnostic testing is offered to patients with symptoms of CF and has been added to the newborn screening programs in 8 states. About two thirds of new cases in the US are in individuals who are <1 year old. A sweat chloride test, nasal potential difference and/or immunoreactive trypsinogen test (used in newborns who may not produce enough sweat), in conjunction with DNA studies, is used to confirm the diagnosis. Prenatal diagnosis using DNA studies can be performed with chorionic villus sampling or amniocentesis at 10-12 or 15-20 weeks of gestation, respectively. Evidence suggests that treating the condition from birth may improve disease management and lung function.

In 2001, the American College of Medical Genetics and the American College of Obstetricians and Gynecologists issued a policy statement regarding screening for CF. Carrier screening should be offered to the following: (1) individuals with a family history of CF, (2) reproductive partners of individuals with CF and (3) couples in whom one or both partners are Caucasian (of northern European or Ashkenazi Jewish decent) and are planning a pregnancy or seeking prenatal care. This allows CF carriers to choose whether or not to conceive biological children and provides them the opportunity to pursue prenatal diagnosis with the option of terminating the pregnancy. Couples should understand that the DNA test cannot detect all mutations; therefore a negative screen reduces, but does not eliminate, the risk of being a carrier.
A multiethnic standard screening panel of 23 CFTR mutations with a US population frequency =1/1000 is recommended. Additional mutations can be added or removed if they reach or fall below this frequency. The screening panel is expected to have a sensitivity of 80% in Caucasians of European decent, 90% in Caucasians of northern European descent and 97% in Ashkenazi Jews. Detection rate in African-Americans and Hispanics is 69% and 57%, respectively. The data for Asian-Americans is unknown. Adding less common mutations results in only very small increases in the sensitivity of screening.

When certain methods are used, the presence of normal genetic variants can cause false positives. To eliminate false positive results, laboratories will perform “reflex” testing for certain positive mutations. These tests are done automatically and do not require additional requests by the referring provider.

It is important to provide the laboratory with the appropriate information, so they can provide the most accurate results. The minimum required data includes: (1) if the test is being ordered to determine affected or carrier status, (2) if there is a family history and (3) the patient’s ethnicity. Diagnostic testing requires the laboratory to identify 2 mutations. If only 1 is found using a screening assay, further testing may be warranted, depending on symptoms and ethnicity.

The issues surrounding CF screening remain complex. There are limitations to the testing itself, as well as in predicting the severity of the disease from the genotype. Despite this there is strong support for screening and early intervention.