New CF Screen Expected to Improve Accuracy

Genotyping test may allow more labs to perform CF screening and allow greater uniformity of result reports.

BY CHRISTINE KILGORE
Contributing Writer

The Food and Drug Administration's approval of a genotyping test for cystic fibrosis detection should improve screening accuracy and availability and could result in more uniform reporting of test results to physicians, experts say.

The new test—coined the "Tag-It Cystic Fibrosis Kit"—is the first multiplexed genotyping test to be cleared by the FDA as an in vitro device for diagnosing human disease.

Laboratories traditionally have purchased what are known as "analyzed specific reagents" and then have had to establish and validate assays and test kits themselves. The newly approved device, on the other hand, is a "standardized, validated testing kit. … It moves us past the 'home brews,' and makes for a more accurate test," said Michael Watson, Ph.D., executive director of the American College of Medical Genetics.

Dr. Watson was a lead author of the clinical and laboratory guidelines for cystic fibrosis (CF) carrier screening that were published in 2001, and updated in 2004, by the ACMG and the American College of Obstetricians and Gynecologists (ACOG).

The kit is approved for use in carrier testing, as an aid in newborn screening, and in confirmatory diagnostic testing in newborns and children.

It can be used to detect and identify simultaneously 39 mutations in the gene for CF—known as the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene—as well as 4 polymorphisms.

These variations include the 23 mutations recommended in the updated ACOG-ACMG guidelines as a "core mutation panel" for carrier screening in the general population. According to the manufacturer, the kit covers additional mutations seen in the African American and Hispanic communities.

"The percent of carriers picked up in [these communities] will go up," said Graham Henderson, marketing manager for Tm Bioscience Corp. of Toronto.

The original 2001 guidelines recommended a standard screening panel covering 25 mutations, but one mutation subsequently was found to occur less frequently than expected, and another was found not to be a true mutation.

Laboratories today typically use the recommended 23-mutation panel and then supplement this, if possible, with tests for such additional mutations when screening particular racial or ethnic groups.

According to the ACOG-ACMG guidelines, the standard "pan-ethnic" 23-mutation panel has an expected sensitivity of 80% in Caucasians of European descent, 90% in Caucasians of Northern European descent, and 97% in Ashkenazi Jews. Even when the panel is supplemented with additional mutations, there is always some "residual risk," or "small possibility of an affected offspring," the guidelines say.

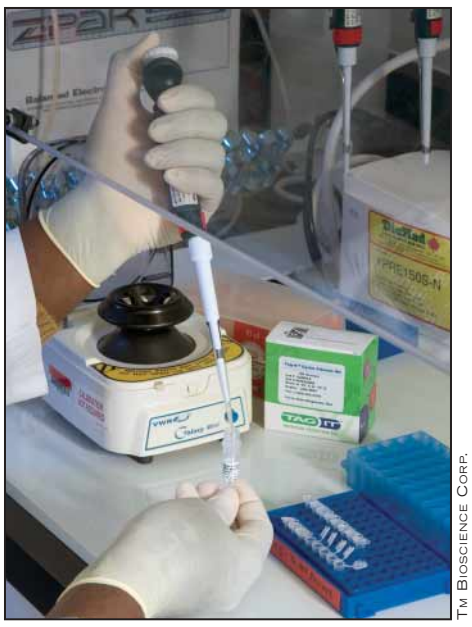
Donna Galehouse, Ph.D., technical director of the molecular diagnostics lab at Akron (Ohio) Children's Hospital, said the new device will enable more labs to perform screening, and will enable them to accurately handle high test volumes.

If use of the device becomes a standard of care, Dr. Watson said, physicians should get more "uniform" test result reports. "Right now, residual risks vary, depending on where testing is done" for instance, he said. "Physicians have to check carefully on what exactly was done and how it translates" into clinical meaning.

According to the ACOG-ACMG guidelines, screening should be offered to couples with a family history of CF, partners of individuals with CF, and Caucasian couples of European or Ashkenazi Jewish descent that are planning a pregnancy or seeking prenatal care.

Information about CF screening should be provided to patients in other ethnic and racial groups, the guidelines say.

A survey done 2 years after the guidelines were first issued showed that the vast majority of 632 ob.gyns.—89% of the respondents—ask obstetric patients about their family history of CF and offer CF carrier screening. Nearly two-thirds offer screening to all prenatal patients.



Tm Bioscience Corp.

The Tag-It Cystic Fibrosis Kit is approved for use in carrier testing and can identify 39 mutations in the CF gene.

In the gynecologic setting, practice patterns were much different. Almost one-half of physicians who responded to the survey indicated that they do not ask nonpregnant patients about their family history of CF or provide them with information about screening (Genet. Med. 2004:6;450-5). (The survey was mailed to 1,165 ACOG members—approximately half of whom participate in the College's Collaborative Ambulatory Research Network, and half of whom were randomly selected.)

Reports on CF screening, according to the guidelines, should include the reported ethnicity of the patient and the indication for testing as well as the mutations tested and the method of testing. Negative screening tests should define "as accurately as possible" the residual risk of the person tested. "This will vary by ethnic or racial group and should be so specified in the test report," the guidelines say.

Since the *CFTR* gene and the most common genetic mutation causing CF were identified about 15 years ago, more than 1,300 genetic variations have been identified in the gene. Many of these, Dr. Watson said, "are rare or private to an individual or family." The newly approved device is not indicated for use in fetal diagnostic or preimplantation testing, and it is not indicated for stand-alone diagnostic purposes, according to a statement issued by the FDA.

Physicians should "interpret test results in the context of the patient's clinical condition, ethnicity, and family history," the statement said. ■

FDA Downgrades the Antiviral Efavirenz to Pregnancy Category D

BY JANE SALODOF MacNEIL
Southwest Bureau

The Food and Drug Administration has downgraded efavirenz to pregnancy category D, "Positive Evidence of Fetal Risk," and is urging women to avoid becoming pregnant while taking the antiretroviral drug.

The new package label stems from four retrospective reports of women who gave birth to infants with neural tube defects after first-trimester exposure to efavirenz (Sustiva). Three infants were diagnosed with meningomyelocele and one with Dandy Walker syndrome.

Physicians are being asked to report pregnant patients who have been exposed to efavirenz to the Antiretroviral Pregnancy Registry (800-258-4263), which was established to monitor fetal outcomes. The drug had previously been labeled category C: "Risk of Fetal Harm Cannot Be Ruled Out."

Bristol-Myers Squibb Co., Princeton, N.J., alerted health care providers to the label change in a letter dated March 2005 and made public in June. Signed by Freda C. Lewis-Hall, M.D., senior vice president for medical affairs, the letter urged pregnancy testing before women start on efavirenz.

"Though there are no adequate, well-controlled studies in pregnant women, Sustiva should be used during the first trimester of pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options," Dr. Lewis-Hall advised. "Barrier contraception should always be used in combination with other contraceptive methods."

There have been four retrospective reports of women who gave birth to infants with neural tube defects after first-trimester exposure to efavirenz.

Dr. Lewis-Hall described a prospective review of pregnancy outcomes for 206 women who carried 207 fetuses, while exposed to efavirenz. Five of 188 infants born after first-trimester exposure had birth defects; none were observed in 13 live births after second- or third-trimester exposures. Dr. Lewis-Hall did not describe the birth defects, except to say they were not neural tube defects, which, so far, have only been seen in retrospective reports.

"Although a causal relationship of these events to the use of Sustiva has not been established, similar defects have been observed in preclinical studies of efavirenz," she wrote. Her letter cited a preclinical animal study that reported malformations in 3 of 20 fetuses from cynomolgus monkeys treated with efavirenz throughout pregnancy.

Gerald G. Briggs, B.Pharm., told this newspaper that data from pregnancy registries and retrospective reports should be viewed as identifying possible signals and raising hypotheses.

"Follow-up controlled studies are needed to determine if the association is causative," said Mr. Briggs, a pharmacist clinical specialist at Women's Pavilion, Miller Children's Hospital, Long Beach, Calif., and coauthor of the reference book "Drugs in Pregnancy and Lactation" (Philadelphia: Lippincott Williams & Wilkins, 2005).

He did not rule out prescribing efavirenz for a pregnant woman who is positive for HIV. If she cannot take an alternative nonnucleoside reverse transcriptase inhibitor and has done well on efavirenz, he recommended continuing her on the drug.

"Taken in sum, the data suggest that there may be a small risk of neural tube defects and other defects, but no neural tube defects were observed in 188 prospective cases, so the risk must be low," he said.

As in all potential pregnancies, he added, the woman should be taking folic acid before conception.

"It may not be preventive," Mr. Briggs said, "but based on the potential signal, I would recommend the same folic acid dose used for anticonvulsants known to cause neural tube defects and for women with a history of giving birth to an infant with a neural tube defect: 4 or 5 mg per day." ■