



Association for Molecular Pathology
Promoting Clinical Practice, Basic Research, and Education in Molecular Pathology

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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
(HFA-305)
Rockville, MD, 20852.
<http://www.fda.gov/dockets/ecomments>.

Ladies and Gentlemen:

The Association for Molecular Pathology (AMP) is a national not-for-profit educational society representing over fourteen hundred physicians, doctoral scientists, and medical technologists who perform molecular diagnostic testing based on nucleic acid technology. AMP members practice their specialty in academic medical centers, independent medical laboratories, community hospitals, federal and state health laboratories, and the *in vitro* diagnostic industry. In this capacity AMP members are involved in every aspect of molecular diagnostic testing, administration and interpretation of molecular diagnostic tests, research and development, and education. For the last several years AMP has provided national leadership for the advancement of safe and effective practice and education for molecular diagnostic testing in the health care industry.

We are delighted that the FDA has issued guidance for manufacturers to support the classification of CFTR gene mutation systems into class II special controls. We have read the document, "Class II Special Controls Guidance Document: CFTR Gene Mutation Detection Systems", issued on October 26, 2005 and look forward to additional cleared products for use by our membership as a means to provide CFTR mutation analysis for carrier screening and as an aid to diagnosis.

CFTR mutation analysis is a complex, multiplex assay. We note that the American College of Medical Genetics (ACMG) has issued guidelines for carrier screening of the general population, recommending a panel of 23 mutations and 4 associated variants (see <http://www.acmg.net/resources/policies/pol-005.asp> and http://www.acmg.net/resources/policies/CF_mutation_8-2004.pdf). The ACMG policy very clearly states that enhanced panels should not be offered nor encouraged for routine carrier screening. We are concerned that the predicate device tests for an enhanced panel of 40 mutations, many with scanty descriptions in the published literature; yet, the Guidance Document does not address mutation panel composition of this device. As ever-expanding probe arrays and multiplex assay products are submitted to FDA for this and other diseases, the agency will face continued challenges in attempting to evaluate claims (explicit or implied) of clinical utility for the individual mutation tests and for their aggregate as a panel. Such a task is extremely complex, often requiring deliberation for years by committees of

experts in the field, or lengthy epidemiologic surveys of allele frequency and genotype-phenotype correlation. Since the required expertise is unlikely to exist within the agency, we recommend that all effort be made to enlist the input of outside experts and professional practice organizations (such as ACMG and the Association for Molecular Pathology) in making these evaluations. Based on this, we recommend that the following sentences be added to Section 5, Risks to Health, Paragraph 3:

“The American College of Medical Genetics recommends that extended mutation panels should not be offered routinely to couples, since they would have the effect of increasing patients' anxiety, would appear to endorse an alternative mutation panel beyond the standard panel defined by the ACMG as the "standard of care" and would provide very low additional yield, leaving such couples who test positive/negative with essentially the same level of uncertainty as they had before. Laboratories offering such panels should clearly state in both their advertising and reporting materials the limited increase in carrier detectability which they provide, basing the additional percentage figures on data from the CF Consortium and CF Foundation Patient Registry Annual Data Reports and/or the proposed CDC CF Database rather than their own data.”

In addition, we wish to comment at length on the sections that address interpretation of results, as detailed below. Overall, we feel that the FDA has equated robust analytical performance with data interpretation and the subsequent laboratory reports of test results for individual patients. The Guidance contains several recommendations regarding reporting of CFTR mutation analysis results. However, the products targeted by the Guidance are used only in the analytic portion of the testing process. Taken as a whole, the guidance implies that the assay result is equivalent to the clinical interpretation of the result, which is not the case. Moreover, it is the opinion of AMP that the diagnostics industry and the testing community would be better served if the Guidance were limited to the analytic phase of the CFTR mutation analysis process. By separating these phases of testing, this document will recognize the role of the Genetics Laboratory Director in interpretation and reporting of results.

Background

The testing process consists of three phases: pre-analytic, analytic and post-analytic. The pre-analytic phase of CFTR mutation analysis includes collection of patient information (indication for testing, patient personal/family history and ethnicity). For carrier screening, this information allows determination of prior risk and Bayesian calculation of revised risk after a negative mutation analysis.

The analytic phase of testing includes determination of the CFTR alleles and genotype present in the patient sample. Herein, a CFTR Gene Mutation Detection System will report the specific presence of zero, one or two mutations in a patient sample as well as reflex variants, as appropriate.

Results are interpreted and reported by the Genetics Laboratory Director in the post-analytic phase. The indication for testing (a carrier study on an asymptomatic patient or a diagnostic test for a symptomatic patient) is critical for test interpretation, since the same test result will have multiple interpretations. Both prior and revised carrier risk after a negative mutation analysis are derived from the ethnicity and the family history of the patient.

The requirements for an appropriate clinical report following CFTR mutation analysis have been addressed by professional societies and regulators, and can be viewed at the websites for the College of American Pathologists and the American College of Medical Genetics. Briefly, these elements include

- An appropriate summary of the methods, the loci or mutations tested, the analytic interpretation, and clinical interpretation.
- Final report review and signature by the director or a qualified designee if there is a subjective or an interpretive component to the test.
- In genetic testing for complex disease genes with multiple possible mutations, an estimate of mutation detection rate and the residual risk of being a carrier for one of the mutations not tested for.
- A discussion of the limitations of the findings and the clinical implications of the detected mutation (or negative result) for complex disorders with regard to recessive or dominant inheritance, recurrence risk, penetrance, severity and other aspects of genotype-phenotype correlation.
- A recommendation that patients receive appropriate genetic counseling to explain the implications of the test result, its residual risks and uncertainties, and the reproductive or medical options it raises, to the patient, where appropriate.

Clearly, the complexity of reporting of CFTR mutation analysis supersedes that professional ability of the device manufacturer to adequately address in a package insert and neglects the role of the Genetics Laboratory Director in this process.

Suggestions for Revision of the Guidance

Section 5. Risks to Health, Paragraph 2

As written, this section does not recognize that the Genetics Laboratory Director is an integral partner in all phases of the testing process and is responsible for laboratory result interpretation and the written report.

Original Text:

“Interpretation of test results depends on many factors, such as patient demographics, family history, and mutation or variants associated with infertility. To aid in a test interpretation manufacturers should recommend in their labeling that test results should be accompanied by genetic counseling. This will enable individuals and couples to receive guidance and information about risks and prognostic factors. CF has a wide clinical variability, with inconsistency of genotype-phenotype correlations for particular mutations. In addition, not all CFTR mutations cause cystic fibrosis. Possible test results that would benefit from interpretation by specialists include results for individuals who have a family history of CF, CFTR mutation carriers including couples where one or both partners are carriers, and otherwise healthy males who carry mutations associated with infertility. “

Suggested Revised Text:

“Interpretation of test results depends on many factors, such as patient personal history, ethnic background and family history. To aid in a test interpretation manufacturers should recommend in their labeling that all test results must be interpreted by a qualified Genetics

Laboratory Director, who is also responsible for the written report and appropriate post-test referrals. This will enable individuals and couples to receive guidance and information about reproductive risks, additional available testing, as appropriate, and prognostic factors. CF has a wide clinical variability, with inconsistency of genotype-phenotype correlations for particular mutations. In addition, not all CFTR mutations cause cystic fibrosis. “

Section 6. Device Description, Test Results/Reporting, Paragraph 1

This section confuses the assay output and the clinical laboratory reports. An example of assay output is the TDAS data summary that is associated with CFTR assays performed on the cleared product from Tm Bioscience. These data display the actual mutations and the associated hybridization signal for each test sample. As such, they are the “raw data” and are basis of the clinical laboratory report written by the Genetics Laboratory Director. Such raw data would not be meaningful to the health professional who has ordered the test; instead, he/she needs a summary of the results and interpretation in the context of pre-analytic variables relevant to the findings for the patient.

Original Text:

“You should provide examples of test reports (e.g., printouts) as would be supplied to the healthcare provider. Reports should be consistent with current recommendations of genetics professional societies, and should contain adequate interpretation guidelines for the use of the ordering physician/counselor.”

Suggested Revised Text:

“You should provide examples of data summaries (e.g., printouts) as would be supplied to the laboratory performing the test. The Genetics Laboratory Director will use these data as the basis for a clinical interpretation. Reports written by the Genetics Laboratory Director should be consistent with current recommendations of genetics professional societies, and should contain adequate interpretation guidelines for use by the ordering physician or genetic counselor.”

Section 10. Labeling. Interpretation of Results

Original Text:

“You should clearly reference any phenotype definitions. We recommend that you provide a section in your package insert to aid users in interpreting test results. The result reports should be consistent with current recommendations of genetics professional societies, if applicable, and should contain adequate interpretation guidelines for the use of the ordering physician/counselor. To aid in a test interpretation manufacturers should recommend in their labeling that test results should be accompanied by genetic counseling. See also the section on Test Results/Reporting, above.”

Suggested Revised Text:

“You should clearly reference any phenotype definitions. We recommend that you state in your package insert that the output from your assay consists of uninterpreted results and that a qualified Genetic Laboratory Director is responsible for test interpretation. See also the section on Test Results/Reporting, above.”

We thank you for your attention to this matter. We look forward to additional cleared devices for CFTR mutation analysis and hope that you will consider the added value of our comments. Please contact Jean Amos Wilson, PhD of the AMP Professional Relations Committee at jamoswilson@focusdx.com for further information.

Sincerely,

A handwritten signature in black ink, reading "Barbara Zehnbauer". The signature is written in a cursive style with a large initial 'B' and a long, sweeping tail.

Barbara A. Zehnbauer, PhD
President