March 28, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Docket no. FDA-2015-N-4809 for "Patient and Medical Professional Perspectives on the Return of Genetic Test Results; Public Workshop; Request for Public Comments"

Dear Sir/Madam:

The American Association for Clinical Chemistry (AACC) appreciates the opportunity to comment on the Food and Drug Administration (FDA) request for public input regarding the format for reporting genetic data to clinicians and patients and the level of evidence that should be provided to make the data interpretable. The Association strongly supports the agency's efforts to ensure that those making medical decisions, and those affected by those decisions, have a better understanding of genetic testing results and their implications.

AACC is a global scientific and medical professional organization dedicated to clinical laboratory science and its application to healthcare. AACC brings together more than 50,000 clinical laboratory professionals, physicians, research scientists, and business leaders from around the world focused on clinical chemistry, molecular diagnostics, mass spectrometry, translational medicine, lab management, and other areas of progressing laboratory science. Since 1948, AACC has worked to advance the common interests of the field, providing programs that advance scientific collaboration, knowledge, expertise, and innovation.

For more than five decades, laboratory professionals have been interpreting and reporting information related to patient test results to clinicians and other authorized individuals. AACC has developed and published practice guidelines to assist laboratory professionals to perform genetic testing and interpret and report genomic results, as have a number of other organizations. Laboratory professionals use these guidelines in their daily practices and routinely communicate their findings to clinicians and patients as part of the care process.

Currently, clinical laboratories performing molecular testing are primarily regulated by private accrediting organizations under the auspices of the Clinical Laboratory Improvement Amendments (CLIA), an oversight model that serves its purpose and should remain in place. Laboratory professionals work diligently to ensure the quality and efficacy of their tests. In addition, laboratory professionals work closely with their physician partners in selecting the appropriate tests, interpreting test results and determining the clinical utility of each selected test. This collegial relationship serves patients and the healthcare community alike and should continue.

AACC agrees with the FDA that patients seeking genetic testing should receive understandable, useful information. It is vital that professional laboratory scientists, clinicians and genetic counselors collaborate with one another to ensure that patients comprehend the purpose of the molecular tests and the implications of the results. Educating physicians on the accurate interpretation of genetic test results is an extremely important aspect of the process. The FDA should work with the healthcare community to develop guidance regarding patient education.

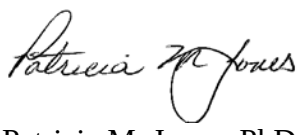
AACC also urges the FDA to take a more proactive role in promoting translational research. This can be accomplished by the agency ensuring that Institutional Review Boards adequately understand the CLIA standards so that they can guide researchers in complying with the CLIA requirements, with which they might not be familiar. Greater FDA involvement may help to enhance the understanding of laboratory regulations within these research facilities while assuring the rights of patients.

In conclusion, AACC recommends that:

- Appropriately trained and knowledgeable healthcare professionals educate patients about the risks and benefits associated with genetic tests;
- Patients be made aware of the financial implications of such testing;
- Test results provided to patients include explanatory language understandable to the lay community;
- Laboratory professionals serve as a resource to clinicians in selecting genetic tests for their patients and interpreting the results and, when appropriate, provide selected literature to assist in care decisions; and
- Patient-centered educational materials be developed by the healthcare community to assist consumers in understanding the value and limitations of genetic testing.

AACC looks forward to working with the FDA as it seeks to improve communication between healthcare practitioners and patients regarding the use of genetic testing information. We are providing more specific information in regards to the case studies discussed at the March 2nd public workshop in the appendix below. If you have any questions, please email Vince Stine, PhD, AACC Director of Government Affairs, at vstine@aacc.org.

Sincerely,



Patricia M. Jones, PhD, DABCC, FACB
President, AACC

Appendix

AACC has received input from member experts on the case studies put forth by the FDA. Their individual responses are provided as bullet points below.

Case Study 2 - Well Patient Tests/Predictive tests

Zoe is a 34 year old Caucasian unmarried woman who does not yet have, but wants, children. Her paternal aunt died of breast cancer at the age of 52. No one in her family that she knows of is of Ashkenazi Jewish descent.

A: You are Zoe. Consider the following:

Do you want to know if you have a BRCA mutation that increases your likelihood of developing breast and ovarian cancer? Do you want to know if you may have other genetic mutations that could increase your likelihood of other cancers? What percentage increase in risk would cause you to consider increased surveillance or prophylactic surgery to remove your breasts and/or ovaries? How would you want to receive this information – from a laboratory or your physician? Or another source? Would major life decisions and estate planning be changed based on the results of your test?

- As a patient with a limited family history of breast cancer, it is important to understand the role of BRCA mutation testing. For example, recommendations from professional societies for indications for BRCA testing, what constitutes a "family history" of breast cancer, and extensive discussion of the potential benefits and limitations associated with testing.

- Whether to consider testing for any cancer predisposition mutations is a highly personal decision. For a patient evaluating mutation testing, a few significant considerations include whether genetic testing is indicated based on a patient's family history, what genes and mutations are included in a test, what the association is between a mutation and predisposition risk, and whether the patient's insurance will pay for genetic testing.

- There is no right or wrong answer as to whether to pursue genetic testing. It is important that a patient understand all factors surrounding a genetic test and provide truly informed consent prior to having a specimen drawn for testing.

- Standard medical practice is for patients to receive laboratory results from the ordering provider. Recreational or direct-to-consumer genetic testing is a noteworthy exception that carries a significant level of risk in a patient who does not entirely understand the test results in the full context of his/her medical care. For example, a patient with a strong family history of breast cancer who does not have a BRCA1 or BRCA2 mutation identified may incorrectly think that he or she has a low likelihood of cancer

predisposition. However, the test may not have included gene deletions. If the patient does not understand that the initial test did not cover the full breadth of mutations, he or she could be under appreciating the risk.

- Estate planning and major life decisions can easily be affected by laboratory results. The intent of informed consent is that these factors are considered prior to making a decision to send testing.

B: You are Zoe's gynecologist.

As you considering ordering these tests, do you consider that Zoe does not have a strong family history of cancer? Do you consider her ethnicity and the population for which the test is validated? Do you want the results of the test? Do you want do know if there are variants of unknown significance? What other information would you like? Would you refer your patient to a specialist? What type? How would you like this information presented? What would you do with it?

- Family history and ethnicity are critical factors to consider when assessing whether to pursue genetic testing. This information should be presented to a patient by someone familiar with informed consent and cancer predisposition testing. The specialist can be a gynecologist who has received specialized training or another provider who has expertise in this area. Clinics at large tertiary care facilities often have specialists who counsel patients for cancer predisposition testing. Their expertise in assessing what type of test – if any – is most appropriate (e.g., targeted testing for a familial mutation vs broad molecular profiling) is essential for patient care. Laboratory reports must clearly identify what types of mutations can be identified as well as accurately describe mutations with HGNC nomenclature.

Case Study 3 – Oncology Tests

Carole is a 63 year old college-educated woman who has a family history of cancer but no known pattern of specific cancers. Her family is of Middle Eastern and Asian heritage. She is diagnosed with lung cancer and has her tumor's genome sequenced.

A: You are Carole.

What information would you like? How would you like it presented? What would you do with it? Consider the following: Your lung cancer has a mutation for an FDA-approved companion therapy for lung cancers. Your lung cancer has a mutation for an FDA-approved companion therapy for breast cancers. Your lung cancer has a mutation that may be connected to higher response rates in prostate cancers. Your lung cancer has multiple mutations that may suggest different courses of therapies.

- A patient diagnosed with lung cancer should be informed of the specific mutation that was detected in tumor specimen and the companion therapy that was FDA approved for

the mutation. In addition, the patient should be told if there are any other therapies available (non-companion) that target the same mutation in my tumor. It is also important for the oncologist to explain to Carole the exact meaning and the implications of "FDA-approved companion therapy." Any information on clinical trials that are available should also be presented to Carole.

- If the mutation is associated with better prognosis in prostate or other cancers, the information may be considered as secondary. However, if there are any targeted therapies in those cancers, the information is useful. Any combination(s) of mutations with therapeutic implications both FDA approved or in clinical trials is information should be documented in the patient's report.

- Detailed information on the potential benefits and drawbacks on the proposed therapy, investigational therapy or clinical trial is necessary. It is important for the oncologist to go over the existing outcomes data on the people who have had the same or similar therapy. The immediate and future implications on health and the financial undertaking should be also discussed.

B: You are Carole's oncologist.

What information would you like? How would you like it presented? What would you do with it? Consider the following: Her lung cancer has a mutation for an FDA-approved companion therapy for lung cancers. Her lung cancer has a mutation for an FDA-approved companion therapy for breast cancers. Her lung cancer has a mutation that may be connected to higher response rates in prostate cancers. Her lung cancer has multiple mutations that may suggest different courses of therapies

- As the oncologist of a patient diagnosed with lung cancer that harbored a targetable mutation, I would evaluate the following information:

    - The exact variant with amino acid and nucleotide information (documented with HGVS nomenclature) and the type of variant – SNV, Indel, structural variant;
    - Gene copy number alterations and/or amplification;
    - The specific exon affected (if relevant – e.g. EGFR, MET…); and
    - In select circumstances, the allelic frequency (may help to determine the germline potential – e.g. TP53 mutations and T790M in EGFR).

  This information would be useful to determine the most appropriate therapy for the patient. For example if the lung tumor had an Exon 19 deletion, then that preferred TKI therapy is afatinib. If the tumor harbors a T790M mutation then osimertinib is the preferred therapeutic indicator.

- Should the tumor harbor a mutation that is a FDA approved companion target in breast cancer, it would be best to look for availability of any clinical trials where the patient meets the criteria for enrollment.

- If the therapies associated with the prostate- and breast-cancer mutation have not been previously documented to be effective in lung cancer, it would be better to first use conventional therapy recommended for lung cancer. If the patient is treatment-refractory, as a second resort, evaluate and consider the possibility of using the therapy that is associated with higher response rates in prostate or breast cancer. The latter is better done in consultation with experts who have experience with similar cases.

- Should the tumor have multiple mutations, the therapy that has shown documented evidence to be most effective would be the better approach.

Case Study 5 - Chronic Disease Tests

Doug is 22 year old Caucasian with a history of depression and schizophrenia that are moderately well-controlled with drugs and therapy. His aunt tells him about a test his doctor can order to help him find the perfect drugs for his conditions by sending in a simple cheek swab.

A: You are Doug.

What information would you like? How would you like it presented? What would you do with it? Consider the following: The data guiding the treatment recommendations is not well-developed. The treatment recommendations are provided as strongly recommended for a number of different options. The treatment recommendations from the test conflict with your current regimen.

- As an informed patient, Doug should seek more information on how the testing is performed – is it marketed as a DTC or offered by a lab with expertise in pharmacogenomics (PGx) testing? Who are the personnel involved? How experienced are they? How is the test interpreted? How was the test validated? Are there any other labs or centers that offer the test? (Many of these questions should be considered by any patient seeking more information regarding the testing being performed.)

- The information received should have an interpretation that can be followed by an informed lay person. It would help to include:

    - The prevalence of the variant(s) with ethnic variation;
    - Conditions directly and indirectly associated with the variant(s);
    - Disease penetrance;
    - Potential therapeutic implications and recommendations; and
    - Contact information for experts and centers of excellence.

- It would be best to take the information back to the treating psychiatrist to see if s/he is able to interpret the results in the specific clinical context. I would ask my psychiatrist to

recommend a physician or a laboratory professional with expertise in interpretation of PGx assays.

B: You are Doug's psychiatrist.

What information would you like? How would you like it presented? What would you do with it? Consider the following: The data guiding the treatment recommendations is not well-developed. The treatment recommendations are provided as strongly recommended for a number of different options. The treatment recommendations from the test conflict with his current regimen.

- The role of PGx testing in the diagnosis and treatment of neurological conditions is still evolving and there are often no documented guidelines. Clinicians should discuss the test interpretation with the patient and explain the lack of standardization and guidance in the interpretation and utility of such testing. Clinicians should also encourage patients to read selected articles from the scientific literature and, where practical, assist the patient in identifying other qualified experts such as genetic counselors and/or laboratory professionals who have specific experience and expertise in the interpretation and application of test results to patient care.

- One underlying concern within this scenario is that many patients are not going to understand the literature regarding the testing or treatment options. Although patients should be encouraged to speak to knowledgeable and experienced healthcare personnel, there is a significant need for patient-centered educational materials to inform patients about the benefits, risks and limitations of genetic testing.