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March 31, 2016

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2015-N-4809

Comments submitted electronically to the docket at www.regulations.gov.

To Whom It May Concern:

Thank you for the opportunity to provide these written comments on behalf of the Association for Molecular Pathology (AMP) to the request for comments in Docket No. FDA-2015-N-4809, "Patient and Medical Professional Perspectives on the Return of Genetic Test Results and Interpretations." AMP is an international medical and professional association representing approximately 2,300 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from the government, academic medicine, clinical testing laboratories, and the in vitro diagnostics (IVD) industry.

Scope of the Workshop:

In its verbal comments, AMP expressed significant concern about the focus of the workshop and those concerns were further reinforced by the discussions that took place on March 2, 2016. While AMP is supportive of the President's Precision Medicine Initiative's approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person, we fail to understand how this workshop contributes to that effort. Additionally, while the agency framed the workshop as part of its contribution to the Initiative, the day's discussions did not focus on returning research results, but rather clinical test results. Given this focus, AMP concludes that comments to this docket will be used by the agency in regards to clinical testing, which may have very significant consequences for patient access to diagnostics.

The scenarios presented in the case studies discussed during the panels do not refer to analytical and clinical validity of diagnostics, but rather to the interpretation of genetic tests and the return of test results to a patient by a health professional. Both of these activities are within the practice of medicine and FDA should not encroach on these practices. In particular, we are concerned that the FDA would limit access to a genetic test simply because the information is non-actionable or the increase in risk associated with the marker is minimal. Information about a clinical condition changes over time, and laboratorians are already well equipped to report out information in a responsible way. Moreover, results that are considered to be non-actionable are not necessarily medically useless at the present moment or in the future; for example, tests results could inform a person's reproductive choices or decision to enroll in clinical research.

AMP believes that these types of decisions around testing and approaches to delivering results are well within the practice of medicine and that preferences for communication of results will vary between individual patients, physicians and clinical circumstances. As such, any policy stemming from the workshop should not intend to subvert decades of clinical, public health and ELSI research, practice guidelines, and other efforts from healthcare professionals on this topic.

Evidenced-based Approaches for Returning Clinical Genetic Test Results and Role of Professional Societies:

The return of genetic test results is not a novel field of research or an emerging practice. For more than five decades since the advent of the Guthrie card and karyotype technology, health professionals have been returning genetic test results to patients and physicians. Early on, much of this experience was in newborn screening and prenatal diagnosis, but as molecular biology techniques and knowledge have advanced, genetic testing has become standard of care for hereditary cancer risk, rare diseases, and many other settings. Along the way, in an effort to inform best practices for returning results, researchers have studied patients' perception of risk, comprehension of genetic information, emotional reaction and coping, and other ethical and social implications of genetic testing. In addition, there are countless professional publications discussing the return of incidental genomic findings, an occurrence that will become the norm rather than incidental as whole-exome and whole-genome sequencing becomes more common practice. All of this research has resulted in a large volume of peer reviewed literature and well-accepted practice guidelines on how best to offer tests and counsel patients on their results, including recommendations that our organization issued in March of 2015.¹ Further, the National Institutes of Health has also held numerous workshops, meetings, and seminars on the very topic. Additionally, the Institute of Medicine (now known as the Health and Medicine Division of the National Academies of Science, Engineering, and Medicine) held multiple meetings on the topic including educating non-genetics health professionals on genetic testing.

AMP believes that activities by clinical practice professional societies, stakeholder conveners such as the Institute of Medicine, and other forms of continuing medical education that examine, educate, and provide recommendations and guidelines for practice are the best mechanisms for consideration on how to best return genetic test results. Professional societies are engaged in providing education for physicians to arm them with capabilities to best care for their patients, including the return of a patient's genetic test results.

AMP recognizes the need for resources across the medical profession for integration and utilization of genetic test procedures into medical practice and works diligently, in collaboration and concert with other professional societies, to address these issues. For example, Molecular Oncology Tumor Boards, an ongoing collaborative effort by the American Society of Clinical Oncology (ASCO), the College of American Pathologists (CAP), and AMP are designed to help cancer care providers with the interpretation and understanding of various tumor molecular profiling tests and studies.² In March 2015, AMP developed recommendations for reporting incidental findings in genomic scale clinical sequencing, which discusses many of the topics examined at the workshop on March 2, 2016 including exploration of potential benefits and harms that could result from different decisions for reporting incidental findings, including the effect on the patient and makes suggestions on how to shape the pretest counseling/informed consent process.³ Additionally, AMP was a collaborative partner with American College of Medical Genetics and Genomics (ACMG) and CAP to develop best practice

¹ [http://jmd.amjpathol.org/article/S1525-1578\(14\)00245-1/fulltext#sec9](http://jmd.amjpathol.org/article/S1525-1578(14)00245-1/fulltext#sec9)

² <http://university.asco.org/motb>

³ <http://jmd.amjpathol.org/article/S1525-1578%2814%2900245-1/fulltext>

guidelines and framework for interpretation and reporting of genetic variants for germline conditions.⁴ AMP is currently leading a collaborative effort with ACMG, CAP, and ASCO representation to develop a similar professional practice guidance manuscript for somatic variants, along with multiple other efforts designed to inform best laboratory practices for clinical NGS.

While the workshop panels included only patients and treating physicians, the importance of a clinical care team in patient management is crucial. Most recently, AMP updated its molecular pathology recommendations for physicians in training programs, recommending residents know how to explain the rationale for and composition of multidisciplinary teams needed for communication of genomic data to patients, of which the role of the pathologist is crucial.⁵ These examples represent valuable contributions to the professional practice of molecular medicine, demonstrating how AMP and other professional medical societies are continuing to add to an already robust collection of peer-reviewed scientific literature that has already been established for returning genetic test results to patients.

AMP is supportive of these efforts within the research community, the clinical practice professional societies, and conveners such as the Institute of Medicine to examine this area and provide recommendations for practice. Because of the wealth of data already available on the topic, it is surprising that the FDA would devote an entire day to discussing case examples that have already been well studied previously. The panel discussions pointed to anecdotal scenarios and circumstances instead of referencing the data and evidence informing best practices, which only accomplished highlighting unsubstantiated fears about how patients integrate genetic information into their healthcare and personal decisions.

Result Interpretation and Communication is the Practice of Medicine:

The interpretation and communication of genetic test results to physicians and patients is the practice of medicine. In a clinical encounter, the practitioner reviews the medical history of the patient and assesses the patient's current state. Using a combination of probing questions based on pathophysiologic understanding of disease and general medical knowledge, the practitioner will choose certain physical examination maneuvers and/or laboratory tests to inform their impression. While performing a physical exam or using diagnostic maneuvers (e.g. auscultation and percussion) the practitioner continually evaluates the incoming data based on their working knowledge of the techniques, giving weight to some data while discounting other findings. The medical practitioner will form a differential diagnosis, evaluate the relative strengths and weaknesses of the competing options, possibly perform research or seek out the opinion of a colleague to aid the decision making process, in order to arrive at a working diagnosis that will direct the next steps in diagnosis and treatment.

Similarly, accredited professionals who are responsible for the design, implementation, and interpretation of the results of genetic testing procedures undertake analogous processes as part of their medical practice. These professionals evaluate the medical history of the patient and the indication for genetic testing. The above includes selected review of the patient records and may include assessment of other laboratory parameters, radiology, or anatomic pathology findings. When the available clinical information is limited, these professionals often contact the treating physician to discuss the clinical situation, clarify any unclear information, and suggest alternative diagnostic methods, if appropriate. After the initial assessment, molecular diagnostic professionals proceed with the analytic process and evaluate the genetic procedure results for each individual patient, taking

⁴ <http://www.nature.com/gim/journal/v17/n5/full/gim201530a.html>

⁵ <http://jmd.amjpathol.org/article/S1525-1578%2815%2900264-0/fulltext>

into account their knowledge of the patient, the diagnoses under consideration, the pathophysiology of the diseases under consideration, and with a keen understanding of the strengths and limitations of the method being used to evaluate the patient.

Although some diseases have a limited spectrum of well-studied genetic abnormalities, all too commonly, the genetic variants that are observed in clinical genetic testing are rare, with limited or absent data to aid in interpretation. For these cases, the molecular professional brings additional information from their expertise, scientific literature, and other data sources to bear on the assessment to help interrogate the data at hand. Similar to a clinical practitioner, the molecular professional synthesizes the available clinical, phenotypic, laboratory, and scientific knowledge to make a determination of the significance and meaning of the available data, which is then composed into a laboratory report to allow for understanding of the result, including the communication of nuances and uncertainties related to the patient and findings. As with most areas within the practice of medicine, there are uncertainties due to limitations such as limited scientific understanding of the observed data, but molecular professionals apply medical judgment in the best interests of the patient, in order to provide maximum benefit, minimize harm, and to advance our scientific understanding of disease.

The activities that occur in the practice of laboratory medicine and pathology, including the performance and interpretation of findings from numerous laboratory procedures, are professional medical services that fall clearly within the scope of practice of medicine and are beyond the purview of the FDA. The inappropriate imposition of regulatory guidelines on the practice of medicine is more likely to cause harm to patients through inhibition of provider-to-provider and provider-to-patient communication and disruption of the high-quality information that patients and providers have come to expect of their laboratory professionals.

Conclusion:

AMP members are already practicing precision medicine every day to improve patient care as they develop, validate, and use laboratory developed testing procedures in all types of diseases including oncology, inherited diseases, infectious disease, and rare diseases. AMP members are a vital part of the clinical care team responsible for providing the patient with a comprehensive understanding of their health, including their genetic test results. As communicated on March 2nd and again in these written comments, AMP believes the questions discussed at this workshop are outside of the FDA's purview and as such, should not inform or be included in any regulatory review processes.

Thank you for the opportunity to submit these comments. If AMP may be of further assistance, please contact Tara Burke at tburke@amp.org.

Sincerely,

Charles E. Hill, MD, PhD
AMP President