



American Society for Investigative Pathology
Investigating the Pathogenesis of Disease

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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 American Society for Investigative Pathology (ASIP) 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." The American Society for Investigative Pathology (ASIP) is a nonprofit educational 501(c)(3) organization primarily representing the academic pathology research community. We are a society of biomedical scientists who investigate disease, linking the presentation of disease in the whole organism to its fundamental cellular and molecular mechanisms. Our members use a variety of structural, functional, and genetic techniques, seeking to ultimately apply research findings to the diagnosis and treatment of patients. Many ASIP members serve in leadership positions providing oversight to clinical laboratory services and also conducting biomedical research utilizing human biospecimens. Our society represents approximately 1,300 physicians and doctoral scientists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes primarily professionals from academic medicine, as well as from the government, clinical testing laboratories, and the *in vitro* diagnostics (IVD) industry.

Scope of the Workshop:

In its verbal comments at the March 2, 2016 Workshop, ASIP provided its views on considerations related to return of research results in genetic testing (attached as Appendix A). Our views on return of research results in genetic testing continue to be particularly relevant given the President's Precision Medicine Initiative.

Except for the initial presentation, the Workshop did not focus on the return of research results. Instead, the discussions centered on clinical test results. Decisions that the FDA will make with regard to clinical genetic testing will have profound effects on patient care and access to diagnostic and prognostic testing. ASIP shares the concerns of several other organizations making public comments during the Workshop; we believe that that the panelists did not provide a comprehensive, focused, and accurate discussion of genetic testing. Pathologists and geneticists, especially those with molecular diagnostic expertise, would have provided critical information relevant to the FDA.

ASIP is also concerned that the scenarios presented in the case studies did 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 we strongly caution the FDA about encroaching on these practices.

Change is rapid as there are new discoveries of somatic mutations leading to cancer, as well as discovery of new drugs correcting or nullifying the effect of the somatic mutations. Determining genetic causation for specific disorders is still a work in progress, and considerable effort will be required to define pathogenicity or lack thereof for specific genomic variants.¹ This is a rapidly evolving field that should be left to further “mature” before strict regulations are put in place that cause harmful delays adversely impacting patient care. A policy should not be viewed as a potential replacement for the individualized integration of personal genetic data with actual patient findings, and informed decisions about patient communication. ASIP has had the opportunity to review the Comments submitted to the FDA from the Association for Molecular Pathology (AMP). ASIP stands together with AMP in believing that decisions around testing and approaches to delivering results are 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 or from the FDA in general should not substitute for 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. There has been extensive research, which is still ongoing, in an effort to inform best practices for returning results, including incidental findings. There are well-accepted practice guidelines on how best to offer tests and counsel patients on their results, including recommendations that AMP issued last year.² Further, the National Institutes of Health has also held numerous workshops, meetings, and seminars on the very topic, and the Institute of Medicine (now known as the Health and Medicine Division of the National Academies of

¹ Manrai AK et al: Clinical genomics: From pathogenicity claims to quantitative risk estimates. *JAMA* 2016; 315(12):1233-34

² [http://jmd.amjpathol.org/article/S1525-1578\(14\)00245-1/fulltext#sec9](http://jmd.amjpathol.org/article/S1525-1578(14)00245-1/fulltext#sec9)

Science, Engineering, and Medicine) held multiple meetings on the topic including educating non-genetics health professionals on genetic testing.

ASIP agrees with AMP that the best mechanism for consideration on how to best return genetic test results are activities by clinical practice professional societies, stakeholder conveners (such as the Health and Medicine Division of the National Academies of Science, Engineering, and Medicine), and other forms of continuing medical education that examine, educate, and provide recommendations and guidelines for practice. Professional societies are engaged in developing education for physicians to arm them with capabilities to best care for their patients, including the return of genetic test results. For example, the American College of Medical Genetics and Genomics (ACMG), AMP, and the College of American Pathologists (CAP) were collaborative partners developing best practice guidelines and framework for interpretation and reporting of genetic variants for germline conditions.³ A collaborative partnership of ACMG, AMP, CAP, and the American Society for Clinical Oncology (ASCO) has begun to develop a similar professional practice guidance manuscript for somatic variants, along with multiple other efforts designed to inform best laboratory practices for clinical genomic testing.

Although the March 2, 2016 Workshop panels included primarily patients and treating physicians and a few genetic counselors, contributions of the entire clinical care team in patient management are crucial. ASIP has been involved with the Training [Pathology] Residents in Genomics (TRIG) initiative since its inception in 2010.⁴ AMP recently updated its molecular pathology recommendations for residents, including the need for the involvement of multidisciplinary teams in the 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 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.

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. When 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 and discounting other findings. The medical practitioner will form a differential diagnosis, evaluate the relative strengths and weaknesses of the competing options, possibly conduct

³ <http://www.nature.com/gim/journal/v17/n5/full/gim201530a.html>

⁴ <http://www.pathologylearning.org/trig/about>

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

further 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.

Although some diseases have a limited spectrum of well-studied genetic abnormalities, all too often the genetic variants that are observed are rare, with limited or absent data to aid in interpretation. Similar to clinical practitioners in direct contact with patients, molecular professionals who practice laboratory medicine synthesize clinical, phenotypic, laboratory, and scientific knowledge to make a determination of the significance and meaning of the available data, which are then composed into a laboratory report. As with most areas within the practice of medicine, there are uncertainties, including limited scientific understanding of the observed data. These considerations and decisions are also increasingly facilitated by the availability of reliable databases, especially on variants of unknown significance, which help diagnostic and therapeutic physicians make the best use of available results. Again, this is an evolutionary process. Molecular professionals who practice laboratory medicine apply their best medical judgment in order to provide maximum benefit, minimize harm, and to advance our scientific understanding of disease. This is, by its very nature, the practice of medicine.

Conclusion:

ASIP 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. Indeed, a past president of ASIP, Stephen J. Galli, MD, was one of the authors of the key report articulating the framework and recommendations on which the President's Precision Medicine Initiative is based.⁶ Like members of other pathology societies, ASIP 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. ASIP agrees with AMP that the questions discussed at the March 2, 2016 Workshop are largely outside of the FDA's purview and as such, should not inform or be included in any regulatory review processes or notice of proposed rule-making.

Thank you for the opportunity to submit these comments. If ASIP may be of further assistance, please contact Dr. Mark Sobel at mesobel@asip.org.

Sincerely,



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Executive Officer

⁶ Desmond-Helmann S, Sawyers CL, Cox DR, Fraser-Liggett C, Galli SJ, Goldstein DB, Hunter DJ, Kohane IS, Llinas M, Lo B, Misteli T, Morrison SJ, Nichols DG, Olson MV, Royal CD, Yamamoto KR: Toward precision medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. Committee on a Framework for Developing a New Taxonomy of Disease. National Research Council of the National Academies. The National Academies Press. Washington, D.C. 2011. www.nap.edu/catalogue.php?record_id=13284.

COMMENTS TO FDA PUBLIC WORKSHOP

**Patient and Medical Professional Perspectives on the
Return of Genetic Test Results**

March 2, 2016

The Pathology Perspective: Return of Genetic Test Results and Interpretations in the Research Setting

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Core Principles

- **Research participants, when receiving their laboratory results, should have confidence in both the results and their interpretation.**
 - **Best Practice: Laboratory results returned to research participants should only come from CLIA-certified laboratories. Recontact to get additional samples should be allowed and not considered, in and of itself, a returnable finding.**
 - **Variance from Best Practice: Should require review by governing IRB.**

Core Principles

- **Research participants deserve the respect of knowing in advance whether and what genetic test results will be returned to them; and, if results are to be returned, the timing and procedure for receiving the results.**
- **Release of individual laboratory results should occur within the same ethical framework developed for the release of other clinical data/observations gathered during a research study.**
 - **Best practice: Inform research participants in advance whether test results will be made available and what the process is for receiving results. Both should be stated clearly in the consent.**
 - **Best practice: Research proposals should proactively address contingencies for findings that may have implications for clinical care.**
 - **Best practice: Inform research participants in advance and as part of the consent process how unanticipated incidental findings will be handled.**

Core Principles

- **Since the primary goal of scientific research is to advance generalizable knowledge, researchers should design and conduct the best possible scientific research within existing ethical guidelines.**
 - **Best Practice: The primary goal of research is not to return individual results to research participants. Where appropriate, researchers may return results provided that:**
 - **Patient safety receives the highest consideration – only VALID (analytical validity, test validity, clinical validity) test results should be returned**
 - **The integrity of the research study is not jeopardized**

Core Principles

- **No hard and fast policy works in all situations. Researchers should seek expert advice when faced with difficult issues.**
- **Best Practice: The governing IRB should work with the researcher to address challenging issues and determine the appropriate course of action:**
 - **Unanticipated/incidental findings with potential clinical care implications**
 - **Return of results from a non-CLIA certified laboratory**

Core Principles

- **Research test results should be maintained separately from the medical record unless:**
 - **testing was conducted in a CLIA-certified laboratory, and**
 - **the informed consent process included this option.**

Core Principles

- **Policies related to Return of Genetic Results in the Research Setting must account for :**
 - **patient safety,**
 - **safeguard the integrity of the research study,**
 - **decreased scientific research funding,**
 - **administrative burden,**
 - **cost implications, and**
 - **the need to ensure research rigor and reproducibility**

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