American Society for Investigative Pathology
Investigating the Pathogenesis of Disease

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Jeffrey R. Botkin, MD, MPH
Chair, Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, The National Academies of Sciences, Health, and Medicine
Associate Vice President for Research Integrity and Chief, Medical Ethics
University of Utah School of Medicine
50 North Medical Drive
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Dear Dr. Botkin:

The American Society for Investigative Pathology (ASIP) appreciated the opportunity to speak on the panel as part of the September 2017 National Academies of Sciences, Health, and Medicine Committee's Meeting on Return of Research Results Generated in Research Laboratories. 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.

We are writing today to expand upon some of the themes discussed during the September meeting. We believe further discussion of these core concerns will serve the Committee well in its final deliberations. We welcome the opportunity to provide additional input or answer any questions.

In its previous letter to the Committee, ASIP outlined the following core principles relevant to the current discussion on returning individual research results generated in research laboratories.

- Laboratories providing results to be used in patient care should be CLIA-certified.
- Different laboratory standards for patient care and for research are appropriate.
- CLIA itself values the difference between reporting of patient test results and research.
- Research proposals should proactively address whether individual-specific research results will be shared and whether these results will be CLIA-certified or not.
- Regardless of whether research is conducted in a HIPAA covered institution or in a non-covered institution, IRBs should carefully consider the issues involved in approving a consent that informs the subject of potential risks and benefits.
- If research results could foreseeably be incorporated into patient care decision making, tests should be performed in a CLIA-certified laboratory. CLIA standards should not be waived when a research subject requests that research laboratory results from a non-certified laboratory be considered in clinical care decisions.

- CLIA-certified laboratories should be the entities responsible for providing information that may, at some point in the future, be used in patient treatment.
- Release of individual research laboratory results should occur within the same ethical framework developed for releasing other clinical data/observations gathered during a research study.
- Even when research is conducted in a CLIA-certified laboratory, ASIP generally discourages the release of individual research results to research subjects because such release would require a costly reporting framework during a period of limited research funds and may leave research laboratories subject to litigation from patients who may not fully comprehended the essential difference between clinical tests and research tests.
- In an era of decreased funding for scientific research, administrative burden and cost implications should be considered when determining an appropriate course of action.
- ASIP believes that individual researchers and their associated IRBs should be the entities tasked with determining whether and under what conditions individual research results will be released to research subjects.

We trust that the following additional discussion points will be useful to the Committee in its deliberations.

Research laboratories are highly diverse, varying widely on such parameters as size, research focus, resources, funding, and capabilities. Regulations must be sufficiently broad to be applicable to all research laboratories. The preponderance of researchers and laboratories speaking at the September Committee meeting represented large, well-funded, genomic research projects. However, ongoing and important contributions are made by laboratories conducting human biospecimen research that is not genomic and could include research in the areas of signal transduction; biochemistry and cell biology of proteins, lipids, carbohydrates, and nucleic acids; gene regulation. As such, the Academy Committee may be well served to provide regulatory commentary on a limited number of issues and recommend best practices or offer recommendations in other areas.

We urge the Committee to request that the US Department of Justice rule on whether 42USC263a (the "CLIA statute") can be interpreted to allow return of individual research results from non-CLIA laboratories without legislative action by Congress. The CLIA statute sought to prevent potentially inaccurate, unproven or misleading information from being provided to patients. Careful legal review is required before abandoning the protections provided by CLIA. ASIP is concerned that the HIPAA rules regarding return of individual research results from non-CLIA certified laboratories are fundamentally inconsistent with the intent of the CLIA statute.

A joint guidance from the involved regulatory agencies would be an excellent step forward. We believe that the following areas are best served by clarifying regulations:

- Allowing (not requiring) researchers to return individual research results obtained in CLIA-certified laboratories;
- Permitting researchers to recommend additional testing to research subjects; and
- Allowing researchers to obtain additional biospecimens in order to utilize a CLIA-certified laboratory to confirm potentially clinically relevant findings.

The Committee should consider whether its conclusions will work equally well for both primary research projects and any secondary research conducted on identifiable biospecimens. The new Common Rule regulations allow for the use of broad consents on identifiable biospecimens. Return of individual research results generated during secondary research conducted under a broad consent pose unique bioethical and practical challenges. When secondary research is conducted, the research subject may have no knowledge of the research project. Being contacted by a researcher may be unexpected and

may seem unrelated to the original research project.

I**ndividual researchers and their associated IRBs should be the entities tasked with determining whether and under what conditions individual research results will be released to research subjects.** In an era of decreased funding for scientific research, administrative burden and cost implications are important elements to consider when determining an appropriate course of action. The decision is best made at this level as it allows researchers and funders to account for any needed, costly reporting framework, ensuring that researchers and funders can make relevant decisions regarding the economical use of limited research funds and account for potential liability concerns. Placing the decision-making obligation at the researcher and institution level also allows each organization to understand the nature of the research being conducted and any unique considerations that may be relevant. If research subjects find that return of research results is critical to their participation in a research project, then subjects will limit their participation only to projects that provide the information.

One option is to develop a set of return of results recommendations applicable to clinical trials and another set relevant for more basic scientific research. While this option is worthy of consideration, ASIP urges the Committee to carefully explore the impact of the relatively new expansion of the definition of clinical trial and associated new regulatory requirements.[1] The policy, effective January 2018, considers a clinical trial to be research involving a human subject and prospectively assigning a subject to an intervention.[2] The broadening of the definition of clinical trial will increasingly encompass research that previously was considered outside of the clinical trial realm.

In general, we recommend the Committee consider issuing a two-part set of conclusions. The first part would focus on regulatory solutions to such issues as the HIPAA/CLIA conflict and disclosure of research results conducted in a CLIA-certified laboratory. See the above paragraph outlining the areas in which regulatory solutions would serve a vital role. The second part of the Committee's conclusions could be recommendations for best practices and situations in which such recommendations would be applicable. Case studies may serve to elucidate some of the proposed recommendations. Examples of such best practices would be the following:

- IRBs should proactively address whether individual research results will be shared; and
- Research plans should proactively address whether re-testing in a CLIA certified laboratory will be appropriate to corroborate a research results and how this process will be handled.

ASIP appreciates the opportunity to raise our concerns with the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories. We hope that our comments may further refine the ongoing discussions. Should you have questions or concerns, please feel free to contact Mark E. Sobel, MD, PhD at (240) 283-9700 or mesobel@asip.org.

Sincerely,

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[1] Hudson KL, Lauer MS, Collins FS Towards a new era of trust and transparency in clinical trials. JAMA. 2016;316(13):1353-1354. Doi:10.1001/jama.2016.14668

[2] https://grants.nih.gov/ct-decision/index.htm

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