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
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Dear Dr. Botkin:

The American Society for Investigative Pathology (ASIP) listened with interest to the June 2017 National Academies of Sciences, Health, and Medicine discussion on return of research results generated in research laboratories. ASIP welcomes the input of this Committee on this important issue. 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.

ASIP believes that it is in a unique position to provide insight on the key issues involved in this discussion. **We request the opportunity to serve as a panelist during the September 6 and 7 workshop.** In particular, we note that Mark Sobel, MD, PhD serves as the Executive Officer of ASIP and has extensive experience both as a Principal Investigator and in representing the issues and concerns relevant to pathology researchers. We have included, as Attachments 2 and 3, Dr. Sobel's biosketch and CV for your reference. Of particular interest to you, please note that Dr. Sobel planned and spoke at PRIM&R's 2016 Advancing Ethical Research Conference on issues such as return of research results and regulatory oversight of pathology research. Per PRIM&R's request, he will co-plan and participate in an updated session at the 2017 AER Conference.

ASIP holds the following core principles relevant to the current discussion on returning individual research results generated in research laboratories each of which is discussed in detail below.

- 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.

Laboratories providing results to be used in patient care should be CLIA certified. ASIP agrees that laboratories performing tests on "materials derived from the human body for the purposes of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of human beings"[1] are appropriately regulated through CLIA. CLIA certification is a key element of safe and effective patient care, supporting the return of the right information on the right patient. CLIA certification should be obtained by laboratories providing information used in the care of patients.

Different laboratory standards for patient care and for research are appropriate. Patient care standards are designed to ensure that the right result is provided to the right patient. Laboratory tests performed in CLIA-certified laboratories must meet analytic (Does the test provide an accurate measurement?) and test validity standards (Does the test measure what it is supposed to?). In addition, CLIA-certified laboratories strive to meet clinical validity standards (Does the test measure a value associated with a clinical condition?). Test results must be reported to the ordering physician(s) with sufficient information for proper interpretation, including false positive and false negative rates and levels of confidence as well as considerations of differential diagnosis. CLIA standards set an appropriately high bar for clinical care and support careful communication allowing for appropriate incorporation of laboratory findings into the care and treatment of patients. The maintenance of CLIA certification requires ongoing substantial investment of training, professional expertise, and administrative oversight. Although the direct cost of applying for CLIA certification is not onerous, the total costs are extremely costly; e.g., revamping all procedures and infrastructure to meet CLIA standards, additional staffing to meet quality control and administrative requirements, and delay in obtaining preliminary results to design effective experiments.

[1] See 42 U.S.C. § 263 a(a)

The goal of research laboratory testing, on the other hand, is to expand upon the generalizable knowledge base. Research sample testing procedures are designed to accurately capture data from specimens in aggregate. In many circumstances, there is no need to correlate results directly with an individual. Furthermore, the research itself may be focused on developing an improved laboratory test and sharing findings would be inappropriate without adequate validation. The ability to conduct research on biospecimens in the aggregate is a cost-effective means of gaining knowledge.

Both the National Institutes of Health[2] and the National Science Foundation[3] have recently expressed concern about the lack of research reproducibility in preclinical research and there are reports in the literature estimating that more than half of preclinical research studies cannot be reproduced. With this in mind, ASIP urges extreme caution in any discussion of return of research results to individuals.

CLIA values the difference between reporting of patient test results and research. Research laboratories are specifically defined as those that "test human specimens but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients…"[4] CLIA also indicates that research facilities may be exempt from certification when performing human specimen research testing that does not provide patient specific results. CLIA standards are applicable, however, in situations in which research tests report identifiable patient specific results that will be or might be used "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings."[5]

Research proposals should proactively address whether individual-specific research results will be shared and whether these results will be CLIA-certified or not. The best practice is to address foreseeable contingencies so that research subjects are made aware, through the informed consent process, of what may occur and what may be required for follow-up, even in rare situations such as an incidental finding that can potentially affect the healthcare of the individual. The research plan should include a contingency plan for those extreme situations in which re-testing in a CLIA- certified laboratory to corroborate a research result may be appropriate and how that process should be approved. ASIP urges a reconsideration of CLIA statutory language that would make it possible to obtain additional biospecimens in order to utilize a CLIA-certified laboratory to confirm potentially clinically relevant results.

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. ASIP believes that this responsibility should be independent of whether an institution is covered under HIPAA. Obligations to research subjects should not vary depending upon the nature of the institution conducting the research. Instead, the nature of the research (clinical care versus research) should be the focus.

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

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[2] Collins F, Tabak LA: NIH plans to enhance reproducibility. Nature 2014, 505:612-613

[3] Reproducibility_NSFPlanforOMB_Dec31_2014.pdf

[4] 42 CFR § 193.3(b)(2)

[5] Research Testing and Clinical Laboratory Improvement Amendments of 1988 (CLIA) Regulations, CLIA Resource, v. 12/10/2014 as accessed on April 7, 2015 from https://www.cms.gov/Regulations-and- Guidance/Legislation/CLIA/Downloads/Research-Testing-and-CLIA.pdf

clinical care decisions. CLIA-certified laboratories are certified for a specific list of tests. Tests provided outside of this scope should not be used in patient care and should be clearly labeled as such. The idea that an individual research result might be used in a clinical context can easily be handled by requiring that laboratories choosing to provide non-CLIA certified tests clearly label such tests with the following or similar statement: "*This laboratory result was generated under experimental protocols for research purposes only without regard to appropriate patient safety and quality control standards and therefore should not be used to affect patient care. Should you have questions or wish to have a test performed as part of your regular patient care, please speak with a physician."* Such a statement would be appropriate when reporting research results from: (i) non-CLIA approved tests performed in a CLIA laboratory; or (ii) tests performed in a non-certified laboratory.

CLIA-certified laboratories should be the entities responsible for providing information that may, at some point in the future, be used in patient treatment. Absent a specific exemption, findings in a non-CLIA certified laboratory, whether or not part of a HIPAA covered entity, should not be used in patient care and this should be clearly stated: (i) in the research proposal that is reviewed by the IRB; (ii) in the informed consent process; and (iii) on any research results that a researcher shares with study subjects. If there is consideration of follow-up of a result from a non-CLIA certified laboratory, an external review should take place prior to the release. The external review should be conducted by the research institution with the support and cooperation of the researcher.

Release of individual laboratory results should occur within the same ethical framework developed for releasing other clinical data/observations gathered during a research study. The release of individual research results should be governed by the broader policy developed in 2016 by SACHRP[6] on the return of individual research results to subjects. This policy set forth a rebuttable presumption of return of individual results. Concerns about research rigor and reproducibility, administrative burden, and potential liability, all of which are discussed in this letter, are critical factors affecting a researcher's (and the sponsoring institution's) ability and willingness to release individual research results. Given the above concerns, ASIP strenuously objects to HIPAA provisions requiring release of research results generated in a HIPAA-covered entity.

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. The potential for legal liability requires a careful discussion and analysis of the costs associated with provision of necessary legal protections to researchers (and their institutions) who voluntarily provide research results. Furthermore, ASIP strongly urges that the return of individual research results be performed through a physician qualified to interpret the research results, including clear identification of risks such as the potential for false positive and/or false negative findings.

In an era of decreased funding for scientific research, administrative burden and cost implications should be considered when determining an appropriate course of action. It is ASIP's opinion that there is little to be gained and much to be lost by mandating that research testing be performed only in CLIA-certified laboratories. This would stifle innovation, dramatically increase costs, and essentially prohibit research on innovative testing modalities.

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[6] Secretary's Advisory Committee on Human Research Protections, Attachment B-Return of Individual Research Results, Letter to the Secretary, July 21, 2016. https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-return-individual-research-results/index.html

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. 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.

ASIP's recommendations are best summarized in a chart presented in Attachment 1, where we note the fundamental distinction between tests to be used in patient care and tests performed solely for research purposes. If tests are to be used in the care and treatment of a patient, the test should be performed in a CLIA-certified laboratory and returned to the patient under HIPAA and CLIA provisions. Tests performed in a CLIA-certified laboratory solely for research purposes may be returned to individuals only under policies that are part of the research proposal and that are clearly communicated to the participant through the informed consent process.

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. **We request an opportunity to serve as a panelist during the September 6 and 7 workshop. We believe that ASIP representatives have expertise in directing research and clinical laboratories and have extensive experience in working with government agencies to represent the issues and concerns relevant to pathology research, including return of research results and regulatory oversight of pathology research.** 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,

Mark E. Sobel, MD, PhD
Executive Officer

Daniel G. Remick, MD
President

Enclosures:
Attachment 1 – ASIP Recommendations – Return of Research Results
Attachment 2 – Biosketch for Mark E. Sobel, MD, PhD
Attachment 3 – Curriculum Vitae for Mark E. Sobel, MD, PhD

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