



**American Society for Investigative Pathology**  
*Investigating the Pathogenesis of Disease*

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November 23, 2015

Jerry Menikoff, MD, JD  
Office For Human Research Protections  
Department of Health and Human Services  
1101 Wootton Parkway, Suite 200  
Rockville MD 20852

Subject: Common Rule NPRM Comment Letter from the American Society for Investigative Pathology; [Docket ID HHS-OPHS-2015-0008](#)

Dear Dr. Menikoff:

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. As such, ASIP believes that it is in a unique position to provide insight to the Office for Human Research Protections (OHRP), DHHS leadership and other federal organizations overseeing human subjects research on the key issues involved in updating the Common Rule for the Protection of Human Subjects (hereinafter referred to as 'the Common Rule').

We welcome the opportunity to discuss our comments further. Should you have questions, please contact Mark E. Sobel, MD, PhD at (301) 634-7130 or [mesobel@asip.org](mailto:mesobel@asip.org).

Many proposals in the NPRM are substantial, positive steps toward reducing administrative burden for investigators, streamlining effectiveness, and balancing the goals of autonomy, justice, and beneficence. Specifically, ASIP endorses the following proposals:

- changes to informed consent rules to increase transparency, specifying information that must be given to prospective subjects and emphasizing the essential information that a reasonable person would want to know in order to make an informed decision;
- broad consents for future unspecified research developed by the Secretary of HHS;

- broad consents used to gather biospecimens in a research setting durable over time;
- the establishment of a safe harbor when researchers utilize a to-be-developed online tool to determine whether a study is exempt;
- the exclusion of new testing assays and quality control from the definition of research where the assay generates information about the subject that is already known;
- the proposals to increase the efficiency and effectiveness of IRBs;
- the proposal to develop standards deemed sufficient to safeguard privacy in addition to those set forth in HIPAA;
- development of a list of activities considered minimal risk by the Secretary of HHS;
- the application of rules on biospecimens in a prospective manner, leaving the valuable collections of archived pathology anonymized or anonymous samples available for current and future research.

**Notwithstanding our endorsement of the above proposals, ASIP is extremely concerned about the proposal to extend the definition of a human subject to non-identified biospecimens, which would have many negative consequences – both intended and unintended.** In addition, there are several areas in which the NPRM proposes treating biospecimens differently from identifiable information. ASIP sees little justification for such differential treatment. Both types of information raise the potential for the unintended revelation of the donor's identity and the subsequent impact that this may have on the individual and their family, including possible employment discrimination, insurance discrimination, embarrassment, stigmatization and other negative effects. No empirical evidence has been offered that biospecimens pose a risk greater than the risk posed for identifiable information. Furthermore, no empirical evidence has been provided that the public is more concerned about or sensitive to the use of biospecimens as compared to the use of identifiable private information. Without such evidence, there is little justification for the path set forth in the NPRM.

**We propose that non-identified biospecimens should be considered in the same manner as identifiable information contained in a medical record. Under HIPAA, individuals are routinely informed of the privacy standards that cover the identifiable, confidential information contained in the medical record. If non-identified biospecimens are redefined as human subjects, we urge consideration of opt-out broad consent models for non-identified biospecimens collected in both research and non-research settings. The American Society for Investigative Pathology (ASIP) believes that, if non-identified biospecimens are redefined as human subjects, an opt-out model would bring consent for the broad use of non-identified biospecimens in line with HIPAA privacy practices, preserving the ability for an individual to decide not to participate in research efforts. Utilization of an opt-out notice for the collection and research use of non-identified biospecimens as part of the privacy notice would be less-burdensome but an inclusive, respectful, and functional way to promote ethically conducted biomedical research on biospecimens. Biospecimens covered under an opt-out model could be tracked in the electronic medical record or the biorepository database. Institutions with limited infrastructure could physically separate biospecimens covered under opt-out from other biospecimens.**

Our areas of concern about the NPRM are listed below in summary fashion.

- Justice and beneficence are important values deserving of equal consideration alongside autonomy, ensuring that all populations benefit from high quality, rigorously conducted human subjects research.
- There has been a significant underestimation of the cost of including non-identified biospecimens under human subjects regulations and the consequent requirement for informed consent. The likely dramatic cost increase may substantially decrease access to specimens, particularly those from minority, rural, and underrepresented populations. This violates the principle of justice since these populations will not benefit from research findings if their biospecimens are not available for study.
- Biospecimens gathered outside of federal wide assurance (FWA) organizations are important to scientific research. The proposed regulations fail to support continued access to these biospecimens while balancing concerns of autonomy, justice and beneficence.
- The proposed standards for waiver of consent for the use of biospecimens would be almost impossible to achieve; furthermore, no evidence is presented that the current approach in the Common Rule has compromised safety for human subjects. Each research project should be viewed independently based on the merits of the scientific knowledge to be gained, weighed against respect for individuals' autonomy and rights to consent. We recommend that the current Common Rule standards be maintained, including: (a) a reasonable scientific rationale for use of the biospecimens; (b) a sound research proposal with the potential to offer scientific advancement; (c) determination that the research is minimal risk; and (d) the research could not be conducted with other biospecimens for which consent was obtained.
- The wording of one particular section,<sup>1</sup> addressing the use of prior collections of biospecimens, is unclear; this statement should be clarified such that archival tissue collections collected prior to implementation of the proposed Common Rule may continue to be used without de-identification in accordance with the original consent. Please see our answer to Question 78.

We were unable to identify a specific NPRM question that addresses problematic assumptions in the cost analysis. Therefore, we have chosen to address these considerations as part of a combined answer to Questions 4 and 5. We have also highlighted these cost considerations in **Appendix A** of this document (see pages 16-17).

**ASIP's concerns and constructive suggestions are consistent with the recommendations of the recently published report of the National Academies of Sciences, Engineering, and Medicine on "Optimizing the Nation's Investment in Academic Research: A New Regulatory Framework for the 21<sup>st</sup> Century."**<sup>2</sup> The National Academies Report points out

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<sup>1</sup> **Federal Register**, Vol. 80, No. 173, Tuesday, September 8, 2015 Proposed Rule, p. 53993.

<sup>2</sup> Committee on Federal Research Regulations and Reporting Requirements: A New Framework for Research Universities in the 21<sup>st</sup> Century, Committee on Science, Technology, and Law; Board on Higher Education and Workforce; Policy and Global Affairs: The National Academies of Science, Engineering and Medicine. *Optimizing the Nation's Investment in Academic Research: A New Regulatory Framework for the 21<sup>st</sup> Century: Part 1*. The National Academies Press, Washington, DC, 2015. ISBN 978-0-309-7822-2 (<http://www.nap.edu/21803>)

the increasing stress on the government-academic research partnership that has been the “principle source of a world-class labor force that has made fundamental discoveries that enhance our lives and the lives of others around the world.”<sup>3</sup> The National Academies Report notes the following:

*“Concerns have been raised repeatedly that federal laws, regulations, rules, policies, guidances, and reporting requirements, while essential to a well-functioning, responsible system of research, have led over time to an environment wherein a significant percentage of an investigator’s time is spent complying with regulations, taking valuable time away from research, education, and scholarship... When effective and well coordinated, federal regulation protects the government, universities, investigators, and the public and helps prevent fraud, waste, and abuse. Today, however, there is a growing concern that the unintended cumulative effect of federal regulations undercuts the productivity of the research enterprise and diminishes the return on the federal investment in research.”<sup>4</sup>*

ASIP appreciates the many aspects of the NPRM that address regulatory burden. However, we are deeply concerned that the proposal to include non-identified biospecimens as human subjects under the Common Rule runs directly counter to the National Academies Report Overarching Finding Two<sup>5</sup> that “continuing expansion of the federal regulatory system and its ever-growing requirements are diminishing the effectiveness of the nation’s research investment by directing investigators’ time away from research and training toward overlapping and incongruent administrative matters that do not take into consideration the environment under which research is conducted at academic institutions today.” Chapter 5 of the National Academies Report points out: “Requiring consent for all research involving biospecimens ... would substantially increase administrative burdens on investigators, research staff, and institutions, and would markedly hinder the conduct of critical science.”<sup>6</sup>

We strongly urge DHHS and fellow agencies to consider RECOMMENDATION ONE of the National Academies Report, which recommends that Congress take actions to direct agencies to “align and harmonize their regulations (and definitions) concerning the protection of human subjects”<sup>7</sup> and to instruct DHHS “to work with other agencies to ensure that research involving biospecimens is eligible for a waiver or modification of informed consent, so long as the proposed research meets the conditions for waiver or modification of informed consent as specified in the Common Rule.”<sup>8</sup>

We also specifically support RECOMMENDATION FOUR<sup>9</sup> of the National Academies Report and call your attention to the specific statements that encourage evaluations of the risk of malfeasance and the overall cost of compliance and that a systemic problem should be

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<sup>3</sup> Ibid, page 1

<sup>4</sup> Ibid, page 1

<sup>5</sup> Ibid, page 3

<sup>6</sup> Ibid, page 69

<sup>7</sup> Ibid, p. 5

<sup>8</sup> Ibid, p. 5

<sup>9</sup> Ibid, p. 8

identified before any new regulation is proposed and that minor issues do not warrant disproportionate responses. Finally, any proposed regulatory changes to include non-identified biospecimens as human subjects and the consequent requirements for informed consent “should be piloted at a small number of institutions to determine whether they efficiently accomplish the intent of regulation, and funds should be provided to pilot institutions for related personnel expenses.”<sup>10</sup>

## ASIP RESPONSES TO SPECIFIC NPRM QUESTIONS

**Question 2. Would providing a definition of biospecimens be helpful in implementing this provision? If so, how might the definition draw a line between when a biospecimen is covered by the Common Rule, and when processing of biological materials (e.g., to create a commercial product used for treatment purposes) has sufficiently altered the materials so that they should not be subject to the regulations? Would only covering biospecimens that include nucleic acids draw an appropriate line?**

The American Society for Investigative Pathology (ASIP) believes that providing a definition of biospecimens would be essential in clarifying the scope of these proposed regulations. We are extremely concerned that defining all biospecimens as human subjects will have negative consequences for research and that the number of biospecimens collected or received in academic medical centers (to say nothing of those collected in organizations such as community hospitals, public health hospitals, clinics, and private physician offices) has not been appreciated. In 2014, over 5 million surgical specimens, over 5 million cytology specimens, and over 3 million hematology specimens were collected by 106 Departments of Pathology and Laboratory Medicine in the United States<sup>11</sup>. These 106 laboratories<sup>12</sup> performed over 544 million tests on the specimens collected for clinical care. The Alternative Proposals would pose a slightly less onerous burden, as the vast majority of collected biospecimens are not used in genomic research, even though they contain nucleic acids.

Defining biospecimens is an extremely complicated issue and worthy of broad discussion. We encourage federal agencies to convene roundtables to solicit input from a range of experts. In particular, ASIP notes its concern with the lack of clarity on whether microbiology specimens, when obtained from a human subject, are considered human biospecimens, since they are often linked with information from the medical record. ASIP is confident that broad input from a variety of stakeholders will allow an appropriate definition of biospecimen to be developed.

### **Combined response to Questions 4 and 5:**

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<sup>10</sup> Ibid, p. 9

<sup>11</sup> Directory of Pathology Training Programs, 47<sup>th</sup> Edition. Intersociety Council for Pathology Information, Inc. ISBN 978-0-937888-30-8, 2014.

<sup>12</sup> The 106 Departments of Pathology and Laboratory Medicine are a subset of the 144 medical schools in the United States. In addition, there are laboratories in community hospitals, public health hospitals, and clinics.

**4. Which of the three proposals regarding the definition of human subject achieves the most reasonable trade-off between the principles of autonomy "including transparency and level of trust" versus beneficence "as measured by facilitating valuable research"?**  
**5. Public comment is sought regarding any concerns that you have about each of the three proposals, including concerns about implementation or burden to investigators and institutions.**

The American Society for Investigative Pathology (ASIP) believes that the current policy exempting anonymous or anonymized biospecimens from human research protections is reasonable and should be maintained. Major scientific breakthroughs have been made utilizing anonymous and anonymized biospecimens for which informed consent was not obtained, without increasing risk to the donors of the biospecimens. In considering the three basic tenets of the Belmont Report – beneficence, autonomy, and justice – we believe that the NPRM puts an inordinate emphasis on autonomy with negative consequences for justice and beneficence. We believe that minimal risk concerns can adequately be addressed by ensuring appropriate levels of data security and information protection for all biospecimen-derived human subjects research. Adherence to high standards for data protection ensures the maintenance of trust while supporting beneficence through the facilitation of valuable research. Respect for the individual's autonomy must be balanced with the substantial benefits that the entire community may receive from scientific progress.<sup>13</sup> Justice and beneficence are important values that deserve equal consideration, alongside autonomy, to ensure that all populations benefit from high quality and rigorously conducted human subjects research.

In several areas, the NPRM proposes treating biospecimens differently than identifiable information. ASIP sees little justification for such differential treatment. Both types of information raise the potential for the unintended revelation of the donor's identity and the subsequent impact that this may have on the individual and their family, including possible employment discrimination, insurance discrimination, embarrassment, stigmatization and other negative effects. No empirical evidence has been offered that biospecimens pose a risk greater than the risk posed for identifiable information. Furthermore, no empirical evidence has been provided that the public is more concerned about or sensitive to the use of biospecimens as compared to the use of identifiable private information. Without such evidence, there is little justification for the path set forth in the NPRM.

If the definition of human subject is expanded to include non-identified biospecimens, we urge consideration of opt-out broad consent models for non-identified biospecimens collected in both research and non-research settings. ASIP believes that an opt-out model would bring consent for biospecimens in line with HIPAA privacy practices, both of which would now be a 'notice' system paired with the ability for an individual to opt out. Such

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<sup>13</sup> Christensen E "Biobanks and Our Common Good," from The Ethics of Research Biobanking, Solbakk JH, Holm S, Hofmann B, editors, New York: Springer 2009, p. 104. ISBN: 978-0-387-93871-4

models have been used successfully in a wide variety of settings. Treating biospecimens more like identifiable information contained in a medical record allows for privacy and information security standards.

The proposed expansion of the definition of human subject to include all biospecimens represents both an unnecessary overreach and a significant cost burden to researchers and their institutions. We are concerned with several faulty assumptions used to calculate the over \$12 billion expected cost<sup>14</sup> for obtaining consent to secondary use of biospecimens and identifiable private information. While it is impossible for ASIP to reconstruct the NPRM's calculation methodology, we believe that the NPRM has underestimated the financial impact of the Common Rule changes by a factor of at least ten. The troubling assumptions are highlighted below.

1. The NPRM assumes that only federal wide assurance (FWA) institutions will store and maintain items for unspecified future research. This fails to account for the significant volume of specimens gathered outside of the FWA environment, including such settings as physician offices, freestanding ambulatory surgery centers, mental health clinics, public health clinics, community hospitals, home health agencies and nursing homes. Many such samples are sent to institutions, both FWA and non-FWA, for analysis or secondary opinions. These specimens are often biopsies of the skin, gastrointestinal tract, or gynecological tissue. The use of non-FWA sites for gathering specimens has an established tradition of federal support and encouragement – one example being the Practice-based Research Network<sup>15</sup> sponsored by the Agency for Healthcare Research and Quality. This Network serves over 24 million patients and operates in all 50 states. Under this initiative, primary care physicians actively participate in research efforts and may represent the frontline provider gathering biospecimens to be used in research. Another example demonstrating the importance of specimens gathered in the community setting is the significant research effort, both past and current, on methicillin-resistant *Staphylococcus aureus* using specimens gathered in the community setting.
2. The NPRM estimates that, per subject, the investigator or dedicated healthcare professional will spend five minutes obtaining broad consent in a research setting and ten minutes in a non-research setting, and that subjects will spend an estimated five minutes engaging in this process in a research setting and ten minutes in a non-research setting. ASIP believes that this is a vast underestimation of the required time commitment. A more appropriate standard for obtaining broad consents, particularly in the startup years, would be 20 to 30 minutes, with additional time and translation resources needed for those individuals whose primary language is not English. Experience with tissue banks has validated this as an appropriate number.
3. The cost projections as developed in the NPRM fail to include the expense incurred should an individual withdraw his or her consent for future research.

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<sup>14</sup> **Federal Register**, Vol. 80, No. 173, Tuesday, September 8, 2015 Proposed Rule, p. 53995.

<sup>15</sup> For more information, please see <https://pbrn.ahrq.gov/>

4. The NPRM has dramatically underestimated the requirements of administering a database to track consents. The average of 1.0 database administrator FTE per institution is grossly underestimated.
5. The cost projections in the NPRM have not included the potential expenditures required to develop a robust database that may be queried by researchers to identify specimens for use in future research projects.

The substantial overall cost, even the gross underestimation included in the NPRM, does not come close to offsetting any perceived autonomy benefits of the expanded definition of human subject, even over a timeline of 10 years. The overall price tag of this proposed regulatory change nets to a cost of over \$10 billion (present value of 10 years at 3% discount rate in millions of \$2013). ASIP believes that many aspects of this regulatory change represent an unfunded mandate with minimal opportunity for institutions to recoup these expenditures. This change comes at a time of limited research funding compounded by substantial cost cutting forces exerted within healthcare delivery.

ASIP also believes that there will be significant unintended consequences as a result of the proposed inclusion of non-identified biospecimens as human subjects. Institutions without significant infrastructure and financial support for collection of biospecimens and for research activities will be unable to establish and maintain the required consent tracking structures. If an institution cannot afford to consent individuals on the 'front-end,' then the biospecimen will not be available for research use, as going back to obtain consent poses significant practical problems, including substantial cost.<sup>16</sup> There are a variety of settings, outside of those institutions with federal wide assurances that contribute valuable specimens today. These include private physician offices, public health clinics, mental health agencies, nursing homes, and community hospitals. The NPRM has failed to address the logistical, operational and financial challenges that will be faced by these institutions should they wish to preserved the ability for biospecimens to be used in future research.

ASIP supports the development of broad consent templates to gather identified biospecimens in both research and non-research (clinical) settings without time limits. Furthermore, if non-identified biospecimens are redefined as human subjects, we urge the use of broad consent to gather non-identified biospecimens. Broad consents would be a less burdensome, but still an inclusive, respectful, and functional way of promoting ethically conducted biomedical research for identified specimens and, if required, for non-identified specimens as well.

Within academic medical centers, the increased administrative and cost burden to obtain informed consent for non-identified biospecimens will disproportionately affect Departments of Pathology and Laboratory Medicine and will further increase indirect costs. Eventually these indirect costs will be built into the cost recovery rate from NIH, thereby reducing funds available for research when the NIH budget is fixed. At a time of

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<sup>16</sup> Bledsoe MJ, Grizzle WE, Clark BJ, Zeps N: Practical implementation issues and challenges for biobanks in the return of individual research results. *Genet Med*, 2012 April: 14(4):478-483. doi:10.1038/gim.2011.67

limited research funding and economic pressures on healthcare delivery, inclusion of all biospecimens under the purview of the Common Rule will serve to deplete the resources available for actual biomedical research.

ASIP is particularly concerned that this regulation may have an unequal impact on many hospitals, clinics, rural healthcare facilities and other healthcare providers that have limited research infrastructure, serve minority populations, and/or care for underrepresented populations. Such entities will most likely have to discontinue biospecimen collection activities, further disenfranchising these communities from the benefits of research. This represents a substantial justice concern. While it is challenging to predict with any certainty, ASIP believes that the proposed Common Rule, as currently structured, favors those institutions with substantial research resources and would likely have a substantial negative impact on disenfranchised communities.

ASIP is also concerned that the proposed expansion of the definition of human subjects to include all anonymized or anonymous biospecimens will have unanticipated, profound consequences on the structure and functioning of biorepositories. We believe that the dramatic increase in administrative burden that would occur under the proposed regulations would virtually eliminate the ability of individual investigators to develop specialized repositories. We believe that the significant administrative requirements of the proposed Common Rule will essentially concentrate the maintenance of biospecimens for secondary research into large, privately maintained collections. Individual scientists wishing to conduct research will be extremely limited in their ability to access the resources available within their own institution and will likely resort to obtaining biospecimens for research from an outside entity – an entity that has the resources to maintain the required administrative structure needed to document consent. Thus, biospecimen resources will be concentrated in the hands of a smaller number of organizations and the cost of accessing such resources will increase dramatically.

**Combined response to Questions 27 and 30:**

**27. Public comment is sought regarding how likely it would be that institutions would allow an investigator to independently make an exemption determination for his or her own research without additional review by an individual who is not involved in the research and immersed in public research protections, (e.g., a member of the IRB staff).**  
**30. Public comment is sought regarding whether relying on the exemption determination produced by the decision tool where investigators themselves input the data into the tool as proposed would reduce public trust in research.**

The use of an online tool to guide the researcher in making an exemption determination will be extremely helpful. However, the American Society for Investigative Pathology believes that many researchers may have difficulties with the nuances of the questions. Guidance should be offered clarifying that the institution in which the research is conducted is ultimately responsible for the conduct of research, and, as such, the institution has discretion to establish an oversight system to assure the appropriate use of the online tool.

**Question 55. Public comment is sought on whether and how the provision regarding the return of research results in the proposed exemptions should be revised.**

The American Society for Investigative Pathology (ASIP) supports involving IRBs in the review of plans to return research results to individuals. The involvement is appropriate in two situations: (1) the researcher plans to return results as part of the research project (preferred option); and (2) the researcher, during the course of research, believes that the return of results is important to participating individual(s). Significant guidance from the Office of Human Research Protections (OHRP) is needed on the complex issues involved in returning results. While most of these issues are outside of the proposed Rule, we wish to bring attention to the well-documented problems with re-contacting individuals.<sup>17, 18</sup>

Concerns about research reproducibility, administrative burden, and potential liability are reasonable concerns that may factor into a researcher's ability and willingness to release research results. Institutional policies concerning the possible return of individual research results to participants should be clearly communicated to research participants as part of the informed consent process.

ASIP remains deeply troubled by the current conflict between the Clinical Laboratory Improvement Act (CLIA) provisions and HIPAA requirements. We believe that HIPAA has been incorrectly interpreted to imply that all research records, when held by a HIPAA-covered institution, must be disclosed to a research participant upon request. We strongly disagree. ASIP believes that only those records that comprise part of the 'designated record set' are those records that must be released by a HIPAA-covered institution upon request. The definition of the 'designated record set' should be updated to clearly reflect that research records are not part of the set unless: (a) the laboratory test was performed in a CLIA-certified laboratory; and (b) there is an anticipation that the research findings will be used in patient care. ASIP has presented its opinion to the Secretary's Advisory Committee on Human Research Protections (SACHRP) in the attached June 23, 2015 letter (**Appendix B**).

**Question 56. Public comment is sought on whether there should be an additional exemption that would permit the collection of biospecimens through minimally invasive procedures (e.g., cheek swab, saliva).**

There should be no distinction between specimens gathered through minimally invasive procedures and those gathered through what might be considered more invasive methods. The determining factor should be the use to which the sample is put and whether new information about the individual donor will be acquired through the research.

**Question 61. Public comment is sought on whether broad consent to secondary research use of information and biospecimens collected for non-research purposes should be permissible without a boundary, or whether there should be a time**

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<sup>17</sup> Bledsoe MJ, Grizzle WE, Clark BJ, Zeps N: Practical implementation issues and challenges for biobanks in the return of individual research results. *Genet Med*, 2012 April: 14(4):478-483. doi:10.1038/gim.2011.67

<sup>18</sup> Wolf SM et al: Managing incidental findings and research results in genomic research involving biobanks & archived datasets. *Genet Med*, 2012 April:14(4):361-384. doi:10.1038/gim.2012.23

**limitation or some other type of limitation on information and biospecimens collected in the future that would be included in the broad consent as proposed in the NPRM. If a time limit should be required, is the NPRM proposal of up to 10 years a reasonable limitation? Would a limitation related to an identified clinical encounter better inform individuals of the clinical information and biospecimens that would be covered by a broad consent document?**

The American Society for Investigative Pathology (ASIP) supports the development of broad consent templates to gather identified biospecimens in both research and non-research (clinical) settings without time limits. Furthermore, if non-identified biospecimens are redefined as human subjects, we urge the use of broad consent to gather non-identified biospecimens.

One of the elements proposed to be included in the broad consent is a description of types of biospecimens collected over what time period. We encourage the phrasing to be general in nature to reflect any and all items collected from the human body; we would discourage phrasing that specifically offered examples or appeared to limit the items covered under the consent.

Whether a specimen is gathered in a research or a non-research setting, ASIP supports the use of opt-out consent for non-identified biospecimens. Such a document should clearly state that non-identified biospecimens may be used for research, now and in the future, and that the individual may decline to give his or her consent by checking a box, initialing, or some other method to be determined. Such opt-out consents have been widely utilized with substantial success.

If there is to be a requirement that consent be obtained for all biospecimens, the structure proposed in the NPRM for specimens gathered in a research setting is reasonable. ASIP requests further clarification on the following issues.

- Does consent cross organizational boundaries such that a multi-institutional system might obtain consent and have it apply to multiple hospitals within the system?
- In multi-site research efforts, what steps will need to be taken when an individual has given consent to Institution A, but has declined to give consent to Institution B?

It is entirely arbitrary and unworkable to gather consent every 10 years for biospecimens obtained in a non-research setting. Placing a time limit on non-research broad consents is as illogical as saying that a retrospective chart review must be limited to the most recent 10 years, eliminating the vast amount of information that could advance science. **We believe that the ten-year limit should be eliminated. Patients can be routinely reminded that broad consents are used regularly and that they may opt-out at any time. Such a reminder can be appended to privacy notices when individuals interact with healthcare providers. Institutions would still be required to maintain a database but it would be much more finite, and focused on tracking those individuals that chose to opt-out or limit access.**

If the system as proposed in the NPRM is enacted, individual institutions will be forced to choose among:

1. developing a system **at the specimen level** for each unique clinical encounter;
2. due to administrative burden, deciding that individuals must either consent broadly for the use of all their biospecimens without limitation or, their biospecimens will not be available for research; or
3. opting out entirely from collecting specimens.

Option 1 is not feasible. If the primary motivation for adopting the proposed regulations is to support an individual's autonomy, ASIP believes that option 2 would undermine that stated goal as it disallows individual participation to those unwilling to enter into all research activities. Option 3 would be unfortunate as it would lead to a decrease in specimens available for research, raising substantial beneficence and justice concerns.

Under the conditions set forth in the NPRM, a tracking system must be able to identify:

- (a) those specimens collected from donors who have consented for the use of their specimens without limitation;
- (b) those specimens collected from donors who have requested limitations on the type of biospecimen that may be used or the use to which it may be put;
- (c) those specimens collected from donors who have declined broad consent for all specimens; and
- (d) those specimens from donors who were not offered broad consent.

Furthermore, where specimens are transferred between institutions, the consent would optimally be provided to the receiving institution (or some other acceptable form of assurance must be established) in order for the receiving institution to be confident that the consent was appropriately obtained and specimens used in accordance with the wishes of the donor.

The significant administrative burden posed by the consent process is another aspect that would further segregate research efforts into those institutions that have the substantial resources needed to obtain consents and those that do not. As discussed above in our responses to Questions 4 and 5, ASIP is deeply concerned about the impact that this requirement will have on research particularly relevant to rural, minority, and other underrepresented populations.

ASIP believes that, when broad consents are used for secondary research, research participants should clearly be informed as to whether or not consent may be effectively withdrawn for future uses. The consent template to be developed by the Secretary must be worded so as to reflect the likely challenges to research associated with withdrawing consent.

**Question 63. Public comment is sought on whether oral consent should be permissible in limited circumstances.**

The American Society for Investigative Pathology (ASIP) does not support use of oral consent when gathering biospecimens, as documenting the oral consent raises too many challenges and may lead to a lack of public trust in the system when there is dispute or misunderstanding concerning the consent.

**Combined response to Questions 66, 67, and 68:**

**66. Public comment is sought on the proposed differences between the criteria for waiving informed consent for the research use of biospecimens versus identifiable information.**

**67. Public comment is sought on whether the proposal to permit an IRB to waive consent for research involving the use of biospecimens should be included in the regulations.**

**68. Public comment is sought on the proposal to permit an IRB to waive consent for the secondary use of biospecimens or information originally collected for research purposes, even if the original research study required subjects' informed consent.**

In several areas, the NPRM proposes treating biospecimens differently from identifiable information. The American Society for Investigative Pathology (ASIP) sees little justification for such differential treatment. Both types of information raise the potential for the unintended revelation of the donor's identity and the subsequent impact that this may have on the individual and their family, including possible employment discrimination, insurance discrimination, embarrassment, stigmatization and other negative effects. No empirical evidence has been offered that biospecimens pose a risk greater than the risk posed for identifiable information. Indeed, the risk for both correlates with the sensitivity of the information. Neither biospecimens nor identifiable information should be treated as proposed in the NPRM.

The regulations, as currently proposed, would require that a waiver of consent may only be granted when there is both: (a) a compelling scientific reason for use of the biospecimen; and (b) research could not be conducted with other biospecimens for which consent was or could be obtained. The bar, as proposed here, would be almost impossible to achieve. Specifically, our concerns include the following.

- How will 'compelling' be determined?
- It is unclear what level of diligence a researcher must document before being eligible for a waiver.
- Establishing the standard requiring that the research cannot be conducted in situations where consent 'could' be obtained offers no parameters for the reasonableness of obtaining that consent. There is no modification such as for situations in which consent could not practicably and foreseeably be obtained.

ASIP proposes that the current Common Rule standards for waiver of consent be maintained, including: (a) a reasonable scientific rationale for use of the biospecimens; (b) a sound research proposal has been developed that has the potential to offer scientific advancement of knowledge; (c) determination that the research is minimal risk; and (d) the research could not be conducted with other biospecimens for which consent was obtained.

**Question 71. Public comment is sought regarding whether particular information security measures should be required for certain types of information or research activities and, if so, what measures and for what types of information or research.**

**Specifically, should the safeguards be calibrated to the sensitivity of the information to be collected?**

The primary risk of research on biospecimens is the potential for unintended revelation of the donor's identity and the subsequent impact that this may have on the individual and their family, including possible employment discrimination, insurance discrimination, embarrassment, stigmatization and other negative effects. In addition, there are privacy considerations, community concerns, and varying perceptions of the relationship between parts, bodies and self-identity. Data confidentiality, integrity, security and controlled access to information should be ensured to maintain donor trust. The American Society for Investigative Pathology (ASIP) is concerned that, as currently proposed, the regulations may have the unintended consequence of actually **increasing privacy risk** by eliminating any incentive to de-identify biospecimens.

All human biospecimens and the information derived therefrom are deserving of the highest level of security. Donors will be more likely to provide tissue samples to researchers who engender trust.<sup>19</sup> ASIP believes that pathologists should support and encourage efforts to develop institutional policies that define how data confidentiality, integrity, security, and controlled access will be ensured.<sup>20</sup> Given the rapid growth of large-scale databases, some of which are publicly accessible, we believe that this is an appropriate area for substantial federal investment to assist in expanding and improving the science of biomedical information security. The regulations have failed to address sanctions for the unauthorized re-identification of subjects. Such standards would do much to reassure the public about professional behavior and responsibilities.

**Question 72. Are the proposed limitations on redisclosure more or less restrictive than necessary? Are there additional purposes for which redisclosure of biospecimens or identifiable private information should be permitted?**

The American Society for Investigative Pathology (ASIP) believes that redisclosure of biospecimens is only appropriate in rare situations in which a confirmed research finding may have significant impact on the health of the donor of the specimen. As we have mentioned in previous correspondence (see Attachment B), 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. Re-disclosure of research information should be permitted as part of re-testing a biospecimen with a potential incidental finding. This is a vital component of responsible treatment of incidental findings. The IRB or other institutional review committee should approve any plans for situations in which corroborative re-testing in a CLIA-certified laboratory may be appropriate.

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<sup>19</sup> Weil CJ, Mechanic LE, Green T, Kinsinger C, Lockhart NC, Nelson SA, Rodrigues LL, Buccini LD: NCI think tank concerning the identifiability of biospecimens and "omic" data. *Genet Med* 2013, 15(12): 997-1003. doi:10.1038/gim.2013.40

<sup>20</sup> Grizzle W, Grody WW, Noll WW, Sobel ME, Stass SA, Trainer T, Travers H, Weedn V, Woodruff K: Recommended policies for uses of human tissue in research, education, and quality control. *Arch Pathol Lab Med* 1999, 123:296-300.

**74. Is mandated single IRB review for all cooperative research a realistic option at this time? Please provide information about the likely costs and benefits to institutions. Will additional resources be necessary to meet this requirement in the short term? Should savings be anticipated in the long run?**

The American Society for Investigative Pathology supports mandatory single IRB review of all cooperative research and recommends that the single IRB of record also be charged with approving the protocol and the consent. The combination of these important functions will ensure that the identified IRB has a full understanding of the research protocol and its potential impact on human subjects.

**Question 78. Is three years appropriate timing to establish compliance with this provision?**

The administrative burdens posed by these new requirements are significant and would require substantial investment in personnel, infrastructure, and financial resources. Particularly as it relates to consent for specimens gathered in non-research settings, we encourage at least a five-year timeframe to allow for appropriate implementation.

The American Society for Investigative Pathology (ASIP) is also deeply concerned about the following wording:

*"Research involving the use of prior collections of biospecimens is permitted if the biospecimens were collected for either research or non-research purposes before the effective date of this subpart, and research use of the biospecimens occurs only after removal of any individually identifiable information associated with the biospecimens."<sup>21</sup>*

The wording of this statement appears to indicate that, even when appropriate consent was obtained at the time of collection for use of the biospecimen in an identified manner or with associated data, prior collections of biospecimens may not be used for future research unless the specimen is non-identified. ASIP requests clarification of this statement such that archival tissue resources collected prior to implementation of the proposed Common Rule may continue to be used in accordance with the original consent.

**Question 79. How often should the Secretary's list of minimal risk activities be updated? Should advice be solicited from outside parties when updating the list?**

The Secretary's Advisory Committee on Human Research Protections should, at a minimum, review this list every three years. The Secretary's Advisory Committee allows for input from outside parties and, with advanced posting of the agendas, the American Society for Investigative Pathology believes this is sufficient.

**Question 80. Is the Secretary's list of minimal risk activities a useful tool for the research community, or does it represent a loss of IRB flexibility in risk determination?**

The American Society for Investigative Pathology strongly endorses the Secretary's provision of a list of minimal risk activities as a useful tool facilitating the IRB review process.

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<sup>21</sup> **Federal Register**, Vol. 80, No. 173, Tuesday, September 8, 2015 Proposed Rule, p. 53993.

**Question 81. What should IRBs consider when reviewing the plans for returning research results, for example, what ethical, scientific, or clinical concerns?**

The American Society for Investigative Pathology (ASIP) believes that this issue is far too complex to be answered in this NPRM. We encourage ongoing discussions at a variety of levels, including extensive involvement of the professional community. We believe that the current structure of the Secretary's Advisory Committee on Human Research Protections does not allow for sufficient outside input. We encourage alternative vehicles that would permit substantial and ongoing interaction with practicing researchers. Possible vehicles that may assist in this process would include roundtables and/or requests for information.

We welcome the opportunity to discuss our comments further.

Sincerely,



Mark E. Sobel, MD, PhD

Executive Officer

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Appendix A - Problematic Cost Assumptions

Appendix B- Letter (June 23, 2015) to SACHRP on HIPAA/CLIA issues

## **Appendix A - Problematic Cost Assumptions: Comments from the American Society for Investigative Pathology (ASIP)**

The proposed expansion of the definition of human subject to include all biospecimens represents both an unnecessary overreach and a significant cost burden to researchers and their institutions. We are concerned with several faulty assumptions used to calculate the over \$12 billion expected cost<sup>22</sup> for obtaining consent to secondary use of biospecimens and identifiable private information. While it is impossible for ASIP to reconstruct the NPRM's calculation methodology, we believe that the NPRM has underestimated the financial impact of the Common Rule changes by a factor of at least ten. The troubling assumptions are highlighted below:

1. The NPRM assumes that only federal wide assurance (FWA) institutions will store and maintain items for unspecified future research. This fails to account for the significant volume of specimens gathered outside of the FWA environment such as physician offices, freestanding ambulatory surgery centers, mental health clinics, public health clinics, community hospitals, home health agencies and nursing homes. Many such samples are sent to institutions, both FWA and non-FWA, for analysis or secondary opinions. These specimens are often biopsies of the skin, gastrointestinal tract, cervix or other gynecological tissue. The use of non-FWA sites for gathering specimens has an established tradition – one example being the Practice-based Research Network<sup>23</sup> sponsored by the Agency For Healthcare Research and Quality. This Network serves over 24 million patients and operates in all 50 states. Under this initiative, primary care physicians actively participate in research efforts and may represent the frontline provider gathering biospecimens to be used in research. Another example demonstrating the importance of specimens gathered in the community setting is the significant research effort, both past and current, on methicillin-resistant *Staphylococcus aureus* using specimens gathered in the community setting.
2. The NPRM estimates that, per subject, the investigator or dedicated healthcare professional will spend five minutes obtaining broad consent in a research setting and ten minutes in a non-research setting and that subjects will spend an estimated five minutes engaging in this process in a research setting and ten minutes in a non-research setting. ASIP believes that this is a vast underestimation of the required time commitment. A more appropriate standard for obtaining broad consents, particularly in the startup years, would be 20 to 30 minutes, with additional time and translation resources needed for those individual whose primary language is not English. Experience with tissue banks has validated this as an appropriate number.
3. The cost projections as developed in the NPRM failed to include the expense incurred should an individual withdraw his or her consent for future research.

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<sup>22</sup> **Federal Register**, Vol. 80, No. 173, Tuesday, September 8, 2015 Proposed Rule, p. 53995.

<sup>23</sup> For more information, please see <https://pbrn.ahrq.gov/>

4. The NPRM has dramatically underestimated the requirements of administering a database to track consents. The average of 1.0 database administrator FTE per institution is grossly underestimated.
5. The cost projections in the NPRM have not included the potential expenditures required to develop a robust database that may be queried by researchers to identify specimens for use in future research projects.



**American Society for Investigative Pathology**

*Investigating the Pathogenesis of Disease*

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June 23, 2015

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The American Society for Investigative Pathology (ASIP) listened with interest to the March 2015 Secretary's Advisory Committee on Human Research Protections (SACHRP) discussion on the current lack of harmony between the regulatory requirements of the Health Insurance Portability and Accountability Act (HIPAA) and the Clinical Laboratory Improvement Act (CLIA). 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. As such, ASIP believes that it is in a unique position to provide insight to SACHRP and DHHS leadership on the key issues involved in this discussion. We request that we be given the opportunity to address the entire Committee at a future meeting so that we can express our opinion and voice our concerns.

We hold the following core principles related to the discussion of disharmony between CLIA and HIPAA regulations, each of which is discussed in detail below.

- Laboratories providing 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.

- Regardless of whether research is conducted in a HIPAA covered institution or in a non-covered institution, Institutional Review Boards (IRBs) should carefully consider the issues involved, approving a consent that informs the subject of potential risks and benefits.
- Research proposals should proactively address contingencies for findings that may have implications for clinical care (incidental findings).
- 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 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 participants because such release would require a costly reporting framework detracting from the economical use of limited research funds and may leave laboratories subject to expensive lawsuits from patients who have not fully comprehended the essential difference between clinical testing 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.

**Laboratories providing 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"<sup>1</sup> 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 (accuracy of a measurement) and test (does the test measure what it is supposed to) validity standards. In addition, CLIA-certified laboratories strive to meet clinical validity (does the test measure a value associated with a clinical condition) standards. 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.

The goal of research laboratory testing, on the other hand, is to expand upon our 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.

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<sup>1</sup> See 42 U.S.C. § 263 a(a)

Both the National Institutes of Health<sup>2</sup> and the National Science Foundation<sup>3</sup> 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 itself 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..."<sup>4</sup> 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."<sup>5</sup>

**Regardless of whether research is conducted in a HIPAA covered institution or in a non-covered institution, Institutional Review Boards (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 is 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.

**Research proposals should proactively address contingencies for findings that may have implications for clinical care (incidental findings).** The best practice is to address foreseeable contingencies so that research participants 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.

**CLIA-certified laboratories should be the entities responsible for providing information that may, at some point in the future, be used in patient treatment.** Findings in a non-CLIA certified laboratory, whether or not part of a HIPAA covered entity, should not be released to individual participants and this should be clearly stated: (1) in the research proposal that is reviewed by the IRB; and (2) in the informed consent process. Where 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 done by the research institution with the support and cooperation of the researcher.

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<sup>2</sup> Collins F, Tabak LA: NIH plans to enhance reproducibility. *Nature* 2014, 505:612-613

<sup>3</sup> [Reproducibility\\_NSFPlanforOMB\\_Dec31\\_2014.pdf](#)

<sup>4</sup> 42 CFR § 193.3(b)(2)

<sup>5</sup> 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>

*American Society for Investigative Pathology Comments – NPRM Common Rule – Docket ID HHS-OPHS-2015-0008*

**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 a broader policy currently being developed by SACHRP on the return of individual research results to subjects. Concerns about research reproducibility, administrative burden and potential liability, all of which are discussed in this letter, are reasonable concerns that may factor into a researcher's ability and willingness to release research results.

**Even when research is conducted in a CLIA-certified laboratory, ASIP generally discourages the release of individual research results to research participants because such release would require a costly reporting framework detracting from the economical use of limited research funds and may leave laboratories subject to expensive lawsuits from patients who have not fully comprehended the essential difference between clinical testing 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 who voluntarily provide research results. Finally, 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.

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. Where 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.

In conclusion, ASIP encourages ongoing dialogue between SACHRP, patient advocate groups and relevant professional associations to develop alternative solutions around this issue. We stand ready to be part of this discussion.

ASIP appreciates the opportunity to raise our concerns with SACHRP and hope that our comments may further refine the ongoing discussions. We request that e be given an opportunity to present our comments at a future meeting of the SACHRP. Should you have questions or concerns, please feel free to contact Mark E. Sobel, MD, PhD at (301) 634-7130 or [mesobel@asip.org](mailto:mesobel@asip.org).

Sincerely,



Mark E. Sobel, MD, PhD  
Executive Officer

Enclosures:  
Attachment 1  
Attachment 2

**RETURN OF RESEARCH RESULTS**

**RECOMMENDATIONS TO ASSIST IN  
RESOLVING CONFLICTS BETWEEN CLIA AND HIPAA**

<b>Laboratory where test is performed</b>	<b>Test result will be used in patient care</b>	<b>Test performed solely for research purposes and will not be used in patient care</b>
<b>CLIA-certified</b>	Return to patient under HIPAA/CLIA provisions	Results should not be returned to participants except as clearly outlined in the research proposal and communicated through the informed consent process. Costs and legal liabilities associated with return of individual results and necessary changes in experimental design must be balanced against potential benefits.
<b>Not certified</b>	N/A	Results should not be returned to research participants and this should be clearly stated in the consent.  In rare situations of an incidental result with potential clinical significance, follow the IRB-approved procedure for external review and possible re-testing in a CLIA-certified laboratory.

## RETURN OF RESEARCH RESULTS

### ILLUSTRATIVE EXAMPLES

#### Example 1

**Study description:** A CLIA-certified laboratory is interested in evaluating whether a new test can better determine which patients will successfully respond to a particular chemotherapy regimen. A key aspect of the research protocol is to correlate the test result with an individual's clinical outcome on a particular standard chemotherapy regimen.

**Approved consent language:** The consent used to gather the specimen was broad and stated that research findings will not be made available to patients.

**Situation arising during the course of research:** During IRB consideration of the study, the question is raised as to whether the results of the test would be included in the patient's medical record.

**Conclusion:** As the new test has not been validated, it is inappropriate to use this test in the course of patient care. As such, the test results will not appear in the medical record of any individual patient and will not be used in the course of patient care.

#### Example 2

**Study description:** A non-CLIA certified laboratory that is part of a HIPAA covered institution is using next generation sequencing to map whole exomes to study Alzheimer's disease. The study requires sequencing both parents and their adult offspring. There is a risk that the study may identify nonpaternity.

**Approved consent language:** The specimens are gathered under a consent specific to the study that states that findings are not disclosed to participants. Risks, including identification of nonpaternity, are explained in the consent.

**Situation arising during the course of research:** A research participant requests the results of his whole exome analysis.

**Conclusion:** The whole exome analysis is not provided.

#### Example 3

**Study description:** As part of a sickle cell hematology study, a non-CLIA certified laboratory performs complete blood counts (CBC) on both identifiable individuals suffering from sickle cell disease and identifiable control subjects.

**Approved consent language:** The consent noted the risk of an incidental finding and described how it would be handled (external review, possible re-testing in a CLIA-certified laboratory, possible re-contact with subject to arrange for re-testing).

**Situation arising during the course of research:** The CBC reveals an incidental finding of significant anemia in a control subject. There is not sufficient sample remaining to have it verified by a CLIA-certified laboratory.

**Conclusion:** Researcher follows the process approved by the IRB and described in the consent: (1) external review of the finding to determine if it warrants corroboration; (2) if so, control subject is contacted by a healthcare provider, asking for permission to verify a potential research finding of as yet uncertain significance; and (3) if permission is granted, control subject is directed to a CLIA-certified laboratory that is part of the same institution for a CBC and follow-up with a healthcare provider. The result obtained by the non-CLIA certified laboratory is not part of the medical record and is not disclosed to the research subject. The report of the CBC obtained in the CLIA-certified laboratory is part of the medical record and can be disclosed under HIPAA.