



American Society for Investigative Pathology
Investigating the Pathogenesis of Disease

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October 19, 2011

Jerry Menikoff, MD, JD
Office of Human Research Protections
1101 Wootton Parkway
Suite 200
Rockville, MD 20852

RE: Docket ID Number HHS-OPHS-2011-0005

Dear Dr. Menikoff:

The American Society for Investigative Pathology (ASIP) is pleased to comment on the advance notice of proposed rulemaking (ANPRM) issued by the Office of Science and Technology Policy (OSTP) and the Office of the Secretary of the Department of Health and Human Services (HHS). ASIP is a nonprofit educational 501(c) 3 organization representing primarily the academic pathology research community. ASIP supports the general objectives of determining how to best protect human subjects who are involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators. ASIP reviewed the ANPRM and developed consensus comments based on the perspective of its members, including academic pathologists and biorepository administrators who are engaged in a range of basic, translational and clinical research in the U.S. and internationally.

As a professional pathology society, ASIP recommends that its members and all biomedical researchers embrace the ethical principles outlined in the Belmont Report by The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979): respect for persons (personal autonomy), beneficence, and justice. Furthermore, ASIP believes that properly constituted Institutional Review Boards (IRBs) provide a bed rock for human research subject protections and the advancement of scientific research.

In reviewing the issues raised by the ANPRM, ASIP focused on questions that are professionally relevant to our membership, specifically issues relating to the use or misuse of biospecimens in research. From these questions, we would summarize the concerns that OSTP and HHS are attempting to address as: 1) whether obtaining informed consent for the research use of all biospecimens, either retrospectively or prospectively, is necessary to assure the patient's (subject's) protection and privacy in research investigations; and 2) whether systems, guidelines and regulations currently exist, or could be strengthened, to ensure patient (subject) protection and privacy without adopting such a comprehensive informed consent process. ASIP believes that to address whether informed consent for all biospecimens is necessary, one must first address whether systems and regulations currently exist or could be strengthened to ensure patient (subject) protection and privacy without uniform informed consent.

The ANPRM references two types of biospecimens:

- Archival (or "left-over") material, collected outside of a research study without the subject's consent for specific research on the biospecimen;
- Research material, collected as part of a specific, rigorous research investigation with the subject's consent.

Regarding *archival material*, the current practice allows research on biospecimens that were collected outside of a research study without obtaining informed consent, as long as the subject's identity is never disclosed to the investigator (*de-identified*). The current system recognizes the value of archival material and the complexities and impracticability of obtaining consent, especially if time has elapsed or a subject is deceased since collection of their material. In our extensive professional experience working with biospecimens on a daily basis, the current system has worked well and has greatly enriched the opportunity for discoveries that were unknown at the time of collection and when research does not require subject identification or involve patient risk.

The current system is governed by the Common Rule (specifically, HHS 45 CFR Part 46.101), the HIPAA Privacy Rule, and the OHRP Guidance on Research Involving Coded Private Information or Biological Specimens (dated October 16, 2008). The key principles in research involving *archival material* that has been anonymized (*de-identified*) are: 1) that it does not qualify as human subjects research; and 2) that there is no intent on the part of the investigator to identify patient (subject) information associated with the archival material. In the event that patient (subject) information is identified, the archival material would revert to stricter rules of human subjects research protections (i.e. *research material*).

Question #11: Advantages of requiring expedited review.

ASIP supports requiring expedited review using the proposed one page summary that would be filed with the IRB before biospecimens are used. IRB approval relieves the pathologist of determining whether the use of biospecimens is appropriate by imparting an experienced, expert, third party review. The brief summary would still provide protection of human research subjects without substantial regulatory burden.

Question #30: Advantages of mandating rather than encouraging a central IRB.

While ASIP agrees that a mandated central IRB could help reduce regulatory burden on some institutions and investigators, especially relevant to the use of biospecimens where there is no more than minimal risk, we have the following concerns: a central IRB would diminish the important concept of sensitivity to local populations and customs inherent in the current local IRB structure, and it would be challenged to abide by all local and state laws and regulations. ASIP does recognize the critical role a central IRB could play in supporting institutions with fewer resources. ASIP therefore supports that a central IRB be encouraged, but not mandated. Perhaps a regional IRB structure would effectively address more of the issues.

Question #47: Change to current practice of allowing research on "left-over" tissue.

ASIP supports continuing the current practice of allowing research on biospecimens collected outside of a research study. Use of archived tissues has made important contributions to medical care. For example, among the most significant advances in colon cancer research in the past decade has been the elucidation of an alternative mechanism for the development of colorectal cancer. This discovery, the serrated polyp pathway, is responsible for 30,000 new cases of colon cancer each year. The initial elucidation of the serrated polyp pathway resulting in mutations causing oncogene activation was accomplished using archived tissues. Loss of ability to use certain types of archived tissues without obtaining consent may be the death knell of live-saving translational research. Other factors that guided our opinion are:

- Requiring informed consent for the collection and use of all biospecimens, including archival tissues, would be tremendously costly for medical institutions to enforce, as assessed by our members at major academic medical centers, including Stanford University and the University of Alabama at Birmingham;
- Because it is impracticable to obtain informed consent for use of all biospecimens in many institutions, much archival and other tissue-based research would be abandoned and many discovery opportunities would be lost;
- Presumed informed consent, with an "opt-out" option, has been considered unethical on the basis that proper education about informed consent is necessary for a patient to lawfully give it;
- Informed consent given by patients "at the door" (a presumed technique of collection to achieve uniform informed consent) may be given under duress of impending medical procedures and could later be legally challenged;
- As described below, strengthening the current regulations and penalties for violation or misuse of archival specimens will go farther to ensure patient (subject) protection and privacy than mandated informed consent for all specimens.

Question #47: (response continued)

- Required informed consent for all biospecimens is an unfunded mandate on research enterprises. How to financially support this mandate must be addressed, yielding to the illegality of using healthcare dollars for research.

Question #48: Permitting waived consent for additional analysis of biospecimens.

ASIP supports allowing waived consent for additional analysis of biospecimens. Archived biospecimens should be considered as de-identified information as defined by the HIPAA privacy rule. ASIP strongly endorses the concept of a general/blanket consent for the use of biospecimens so that such consent will be durable from one research study to another.

Regarding *research material*, the current practice allows research on biospecimens that were collected for specific research purposes with informed consent, which is strictly governed by the Common Rule (specifically, HHS 45 CFR Part 46.116), institutional IRB, and the letter of recommendations from the Secretary's Advisory Committee on Human Research Protections (SACHRP) to Secretary Leavitt (dated January 31, 2008). The current system closely regulates the process of obtaining informed consent and the systems that protect the subject's identity from disclosure (*de-identification*). Again, based on our experience, the current system has sufficient safeguards that are rarely violated. In the rare situations where violation has occurred, informed consent in and of itself would not have prevented the event or protected the subject. Therefore, governing bodies must seek to enforce stronger, clearer regulations and penalties for violation.

Question #49: Is it desirable to implement a standardized consent form for future research?

ASIP understands the ideal of a standardized informed consent form, and encourages the use of a standardized consent form. However, we strongly caution against future rulemaking that requires it for the same reasons that we are not in favor of mandating a central IRB. A required standardized consent form would not effectively respect the unique concerns of special populations (such as Native American, among others). ASIP therefore recommends the following:

- Several institutions have developed consent templates that ASIP recommends for use in the U.S. Those institutions include M.D. Anderson Cancer Center, Roswell Park Cancer Institute, University of Michigan, and H. Lee Moffitt Cancer Center and Research Institute.
- Development of a standardized informed consent form should remain in the realm of the professional community, which will take responsibility to modify it regularly as needs change, versus a Federal regulatory framework, which will remain static for many years.
- The use of a standardized informed consent form should be encouraged but not required.
- Appropriate training and careful monitoring of all relevant staff (including admissions staff of hospitals) will be necessary in order to ensure that true informed consent is obtained when using any informed consent form.

Additional related concerns include:

Agency Inconsistency: For harmony to occur, revisions to the Common Rule must be proposed by each of the 15 original agencies and currently it is only proposed by HHS. Inconsistency in policy would be detrimental to the current processes and would undermine the current assurances of privacy and protection, which have remained rather stable over the past 20 years.

Pediatric Consent: If standardized informed consent is adopted, the particular complexity of consenting minors that reach the age of majority at some point between the start of the original research study and its completion, or the start of future research studies associated with the archival material, will have to be addressed.

Question #52: Should new consent rules only be applied prospectively?

ASIP believes that if new consent rules are developed, they should only be applied in a prospective manner. All current anonymized (de-identified) archival specimens should remain available for use under the current policies.

Questions #56 and 57: Should biospecimens or genomic information be considered identifiable in and of itself?

ASIP does not support the concept that biospecimens are identifiable in and of themselves. Prospectively, as the era of genomic medicine advances, there are public concerns that *archival material* and *research material* contain DNA that makes these samples inherently identifiable. However, DNA molecules and other biospecimens do not identify individuals without some *a priori* knowledge (or other linked information) about the individual or their relatives. For example, it is currently impossible to identify an individual based on a DNA sequence unless there are known DNA sequences from that person or a close biologically related person available for comparison. This is similar to the case of a fingerprint, in which case the fingerprint is not identifiable unless those fingerprints are already present in a searchable database with identifying information. Since the sample has already been collected, the main risk to research subjects is the inappropriate release of information. Therefore, protecting the information is where the regulations and guidelines should be more clear and consistent, and the penalties for violation more strict and deterrent. While there are some databases that contain genomic DNA sequences, and we presume such databases will continue to be developed, a researcher's use of such a database with the intent to identify a specimen would constitute a violation of the use of de-identified specimens, would not be considered minimal risk, and the research would require informed consent. Just as looking up a research subject's information without IRB approval is not allowed, similar bans should be made on any attempt or intent to identify a subject by their genomic data. Again, informed consent in and of itself cannot guarantee privacy protection. Enforcing and strengthening penalties against violations of the Genetic Information Nondiscrimination Act of 2008 (GINA law), specifically the OHRP Guidance on the Genetic Information Nondiscrimination Act: Implications for Investigators and Institutional Review Boards (dated March 24, 2009), will go farther toward providing actual protection.

Question #59: Would subjects be protected from informational risks if strict data security standards modeled on HIPAA rules were applied?

ASIP believes that subjects would be protected if strict data security standards were applied, modeled on HIPAA rules.

In summary, ASIP's view is that the enforcement of current policies regarding the use or misuse of biospecimens coupled with stricter penalties for violations will best ensure protection of human subjects who are involved in research. Required informed consent for the use of all biospecimens, including de-identified specimens, is an ideal that may prove impracticable to achieve for reasons outlined above and represents a disproportionate concern relative to realistic risk. Therefore, expanded requirement of informed consent for all biospecimens will not achieve the goals of facilitating valuable research, while reducing burden, delay, and ambiguity for investigators. Moreover, if the greatest intent of this rulemaking is to guard against the re-identification of genomic data that has been de-identified through research practices, ASIP specifically recommends prohibiting any attempt to re-identify de-identified tissue or to use genomic information outside the legal medical structure (i.e., without informed consent), in lieu of a requirement to obtain informed consent for the use of all de-identified archival tissue.

ASIP sincerely hopes you find these comments constructive and useful in your deliberations. If you need further information or counsel on the points raised in this letter, please contact me.

Submitted by,



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