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ASIP Responds to the Advance Notice of Proposed Rulemaking on Human Subjects Research Protections

The American Society for Investigative Pathology (ASIP) recently responded to 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) on July 22, 2011 concerning the so-called "Common Rule" that governs human subjects protections. The full ANPRM can be found at: http://www.hhs.gov/ohrp/humansubjects/anprm2011page.html. Comments were developed through a joint review by the ASIP Public Affairs Working Group and experts, including, among others, members of ASIP's Division, the International Society for Biological and Environmental Repositories (ISBER). The team developed consensus comments, based on their perspectives as academic pathologists and biorepository administrators, who are engaged in a range of basic, translational and clinical research in the U.S. and internationally.

In general, ASIP supported the ANPRM's objectives of re-evaluating how to best protect human subjects who are involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators. In reviewing the many issues raised by the ANPRM, ASIP focused on questions relating to the use or misuse of biospecimens in research. The response summarized the concerns that OSTP and HHS are attempting to address: 1) whether obtaining informed consent for use of biospecimens (including de-identified) is necessary, either retrospectively or prospectively, to assure patients' (subjects') 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 informed consent for collection of all biospecimens. ASIP framed its response in the following context: to address whether informed consent for use of 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 requiring informed consent for archival or "left-over" specimens.

The ANPRM referenced 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. ASIP commented that in its membership's extensive professional experience in working with biospecimens on a daily basis, the current system (for research that does not require subject identification or involve patient risk) has worked well and has greatly enriched the opportunity for discoveries that were unknown at the time of collection. ASIP noted 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*).

ASIP expressed strong support for continuing the current practice of exempting or allowing waived consent for research on biospecimens collected outside of a research study. Archived biospecimens should be considered as de-identified information as defined by the HIPAA privacy rule. ASIP noted that use of archived tissues has made important contributions to medical care and is a bedrock of translational research. 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. ASIP expressed overwhelming concern for the devastating impact that requiring consent on archival material would have on pathology research and the ability to do small, currently low-cost pilot studies to identify biomarkers predictive of response to selected therapies or to investigate potential mechanisms of pathogenesis. Most if not all of these types of studies are initially performed on archival samples to test the assay, vet the concept, and determine feasibility of a larger study. Imposing such a significant regulatory burden on exploratory studies will clearly impact the ability to rapidly assess new ideas and concepts, and yield little if any tangible benefit.

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 IRBs, 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 ASIP's 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.

Most importantly, ASIP did not support the concept that biospecimens or genomic information 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. 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, ASIP commented that informed consent in and of itself cannot guarantee privacy protection. They stressed that 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.

As a professional pathology society, ASIP recommended 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 IRBs provide a bedrock for human research subject protections and the advancement of scientific research.

ASIP supported requiring expedited review using the proposed one-page summary that would be filed with the IRB before biospecimens are used. ASIP commented that 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. However, ASIP cautiously supported mandating a central IRB to reduce regulatory burden on institutions and

investigators. This is particularly relevant to the use of biospecimens, where there is usually no more than minimal risk. Although ASIP supported the idea of a central IRB, it expressed concerns that a central IRB would diminish the important concept of sensitivity to local populations and customs inherent in the current local IRB structure A central IRB would be challenged to abide by both state and national laws. ASIP recognized the critical role a central IRB could play in supporting institutions with fewer resources and suggested that a regional/central IRB structure might effectively address all issues. If the central IRB concept is pursued, how uniformity of practice will be achieved is a concern that must be addressed.

Regarding implementing a standardized consent form for future research on all biospecimens, ASIP said it respected the ideal of obtaining informed consent, but strongly cautioned against future rulemaking that requires it. ASIP explained that the following issues needed to be taken into consideration:

- requiring informed consent for all specimens 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 consent;
- informed consent given by patients “at the door” (a presumed technique of collection to achieve uniform informed consent) is given under duress of impending medical procedures and could later be legally challenged;
- as described below, strengthening the current regulations and penalties for violation will go farther to ensure patient (subject) protection and privacy than requiring informed consent for the collection and use of all specimens.

If standardized informed consent is pursued for use of biospecimens, ASIP recommended 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 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.
- Appropriate training and careful monitoring of all relevant staff (including hospital admissions) will be necessary in order to ensure that true informed consent is obtained.

Additional related concerns included:
Agency Inconsistency: For harmony to occur, so that consent is truly uniform for the collection and use of all biospecimens, 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 informed consent is adopted, the particular complexity of consenting minors who 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.

Research Limitations: If informed consent is adopted for all biospecimens, the durability of such consent from one research study to another must be addressed for the use of biospecimens that fall outside of the research realm of the original research.

Unfunded Mandate: As currently proposed, a new requirement to obtain 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.

ASIP did not specifically address data security standards, but supported the notion that subjects would be protected if strict data security standards were applied, modeled on HIPAA rules.

In general, ASIP's view was that the enforcement of current policies regarding the use or misuse of biospecimens coupled with stricter penalties for violations, would best ensure protection of human subjects who are involved in research. Requiring informed consent for the collection and research use of all biospecimens is an ideal that is impracticable to achieve for reasons outlined above. Therefore, requiring informed consent for use of 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, in lieu of a requirement to obtain informed consent for the use of de-identified archival tissue.

If you have any questions or comments about ASIP's response to the ANPRM on Human Subjects Research Protections, please contact. The full response letter can be found at: *http://www.asip.org/paffairs/pubaffairs.htm*.

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