COLLEGE of AMERICAN PATHOLOGISTS

Comments to the
Department of Health and Human Services (HHS)
Office of Human Research Protections (OHRP)
On the
Federal Policy for the Protection
of Human Subjects

(**HHS-OPHS-2015-0008**)

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The College of American Pathologists (CAP), the nation's largest association of Board certified pathologists, appreciates this opportunity to provide comments on the *Federal Policy for the Protection of Human Subjects (Common Rule)* that is intended to modernize, strengthen, and enhance the current human research regulations. The CAP, *celebrated 50 years as the gold standard in laboratory accreditation,* is a medical society serving 18,000 physician members and the global laboratory community. It is the world's largest association composed exclusively of board-certified pathologists and is the worldwide leader in laboratory quality assurance. The CAP's Laboratory Improvement Programs, initiated 65 years ago, currently has customers in more than 100 countries, accrediting 7,700 laboratories and providing proficiency testing to 20,000 laboratories worldwide.

The CAP also started the Biorepository Accreditation Program (BAP) four years ago. The only program of its type in the USA, it provides the means to attain and maintain standardization and confidence that biorepositories are following best practices, resulting in high quality specimens obtained under proper regulatory guidelines used to support research, drug discovery, and personalized medicine. At this time, 42 biorepositories are fully CAP BAP accredited with thirteen more in the process of obtaining accreditation.

The CAP BAP and Surgical Pathology Laboratories, our laboratory partners in biobanking that represent the largest de facto human tissue biorepositories, promote high standards for the procurement, processing, storage and distribution of biospecimens that align with quality best practices in the biorepository field to support scientific research. Together, these two groups play critical roles in supporting the majority of existing human tissue research that occurs in the United States. Some of our accredited biorepositories function under broad consent protocols, but others facilitate cooperative group clinical trials, individual tissue acquisition protocols, and honest broker arrangements for accessing, curating, annotating, and de-identifying archival human biospecimens. Under the current rules, such archival tissue is used for basic scientific research, biomarker development, and diagnostic assay development and other vital research. Specifically, we note that archival tissue collections are vital for the study of rare diseases and racial disparities in disease.

The CAP applauds the goals of the Office of Human Research Protections (OHRP) to increase human subject's autonomy in order to make informed decisions by streamlining the human research rules; however, we believe the proposal contains too many complex issues that should be addressed individually through separate rulemaking, in particular the issues associated with the inclusion of biospecimens as human research subjects. It is imperative to have regulations governing human research that balance human protection enhancements and impose minimal burden on researchers. The increased use of sophisticated analytical techniques and the growing use of electronic health data and other digital records will enable very large data sets to be analyzed and combined in novel ways. The CAP supports many of the provisions with the proposed rule such as for the ability to use broad consent for future unspecified research; informed consent rules changes that increases transparency for prospective patients; the ability of broad consents to be used in order to gather biospecimens in a research setting to be durable over time; exclusion from the definition of research new testing assays and quality control and quality assurance materials; exclusion of non-identifiable biospecimens collected prior the compliance date; and a list of activities considered minimal low-risk research. However, the CAP remains concerned about the inclusion of biospecimens regardless of whether these specimens contain non-identifiable information in the definition of human research.

REDEFINING HUMAN RESEARCH

The notice of proposed rulemaking (NPRM) proposes to include in the definition of "human subject" individuals about whom an investigator conducting research obtains, uses, or analyzes biospecimens regardless of whether

or not the biospecimen contained identifiable information. While the CAP strongly believes informed consent should be obtained as part of the general surgical process, we are concerned about the broad inclusion of biospecimens in the definition as human subjects. Pathologists interact with specimens in many ways, but are primarily involved—in the laboratory setting--with the evaluation and diagnosis of blood, body fluids or tissue specimens. These evaluations usually have prognostic implications. Once these evaluations are completed, there are, in many instances, residual specimens remaining. The expansion of these human research requirements potentially will diminish the effectiveness of researchers by requiring overlapping and incongruent administrative activities that are counter to research activities conducted within academic institutions today.

Therefore, we believe if the OHRP elects to move forward with including biospecimens in the definition as human subject research that the OHRP:

- **Allow for informed consent to be obtained as part of the general surgical process;**
- **Waive or exempt non-identified specimens from the proposed rule; and**
- **Agree research with non-identifiable biospecimens collected prior to the compliance date of that provision will continue to be outside of the scope of the Common Rule.**

EXCLUDED CATEGORIES FROM THE COMMON RULE

The NPRM identifies eleven "excluded" activities that are outside the scope of the Common Rule. These activities are generally not considered human subjects research under the Common Rule, or are otherwise low-risk and do not require the Common Rule's full battery of human subjects protections. These eleven exclusion categories are not exhaustive; activities that do not meet the definition of "research," or do not involve "human subjects" as defined by the Common Rule, would also be "excluded." **The CAP strongly supports the proposal including:**

- **Certain quality assurance or improvement activities involving the implementation of an already-accepted practice to improve the quality or delivery of health care; and**
- **The secondary research use of non-identifiable biospecimens where no new information about an individual is generated.**

The pathologist is the laboratory's custodian of these residual specimens. Some portion must be retained, for varying lengths of time, in compliance with federal and state laboratory practice laws. Residual specimens are also needed by clinical laboratories to conduct quality assurance-quality control (QA-QC) activities mandated by the federal Clinical Laboratory Improvement Amendments (CLIA) and implementing regulations, 42 C.F.R. Part 493, as well as by the CAP Laboratory Accreditation Program (LAP). For example, the CAP LAP requires that all new lots of regents be checked against previous lots before being placed into use. A residual patient sample is required to perform this check. Clinical laboratories run a myriad controls such as immunohistochemistry (IHC), Grocott-Gomori's (or Gömöri) methenamine silver (GMS), Acid fast bacteria-Kinyoun's (AFB), and Iron daily for laboratory tissue assays and instrument validation studies. As the pathologist does not interact with the patient for whom these tissue samples were derived, he or she has no ability to ensure that consent for future research uses properly obtained at the time of collection. **The CAP believes clarity is required on the specific entity or person who should have the obligation to ensure that appropriate consent was obtained for the research use.** Pathologists should have no liability should the research or front-line provider responsible for patient intake final to ensure that adequate consent was obtained prior to initiating a research study.

EXEMPTED CATEGORIES FROM THE COMMON RULE

The NPRM proposes to expand the Common Rule's current list of exempt research categories from six categories to eight categories. These exempt activities would not have to comply with all Common Rule requirements, and

would be exempt from certain requirements based on the exemption category. Notable new exemption categories for pathology are as follows:

- Most secondary research uses of identifiable private information collected in a non-research (e.g., clinical) context, when subjects were notified upfront their information could be used in future research;
- The storage or maintenance of biospecimens and identifiable private information for future secondary research uses, when for most samples broad consent is obtained using a standardized template (to be developed by the HHS Secretary); and
- The secondary research use of biospecimens or identifiable private information, properly stored for such purposes, provided written upfront broad consent was obtained using the Secretary's template.

Given the above, the CAP has concerns specifically about the implementation of definition change retrospectively, specifically regarding access to paraffin archival materials. The CAP proposes that samples collected prior to the effective date of the new rule continue to be available under exemption if they are de-identified by an honest broker. We further suggest the provision for use of prior collections of biospecimens at 101(k)(2) be combined with the ability to carry out secondary research with identifiable private information that has been collected for clinical purposes if specific conditions are met. Such facilitation should continue through waiver of consent as administered by local IRBs. Standards of practicability should continue to be used, adding the ability to conduct the research with biospecimens for which there is broad consent. Our experience supports that many scientific questions, including some addressing gender and racial disparities, will continue to rely on broad access to these retrospective, archival specimens.

SECONDARY USE OF BIOSPECIMENS BROAD CONSENT REQUIREMENTS

The regulation of secondary research use of biospecimens and private information is a central focus of the NPRM. As the NPRM would expand the definition of "human subject" to include all biospecimens, the NPRM also proposes changes to facilitate biospecimen research. In particular, the NPRM proposes to allow researchers to obtain a one-time upfront broad consent that would cover (1) the storage or maintenance of biospecimens (as well as identifiable private information) for secondary research use and (2) the use of such stored material for subsequent secondary research studies.

As the NPRM would allow the broad consent to cover the storage and maintenance of biospecimens and identifiable private information in existence at the time of consent as well as information collected in the future, the NPRM would limit such broad consent for future collections of biospecimens and identifiable private information originally obtained for non-research purposes to a 10 year window from when the broad consent was signed.

The CAP recognizes the demonstrated desire of American citizens to exercise more autonomy over the use of their biospecimens. We believe that institutional broad-consent biorepositories created in alignment with Pathology and Clinical Laboratories represent the best path forward and highlight that many of the requirements for CAP BAP accreditation ensure such vital partnerships exist. Our experience in biorepository accreditation suggests that time is required to develop biorepositories that adhere to best laboratory practices. Our experience with existing broad consent biorepositories suggests that organizational complexity and high startup costs present institutional barriers to the development of global informed consent programs for excess tissue donation. We therefore propose extension of the three year transition period to 10 years for phase in of this requirement.

Finally, our experience suggests that institution-wide broad consent programs benefit from direct information campaigns that educate patients and encourage consideration of specimen donation for the benefit of research.

Such campaigns may have the effect of increasing trust and ensuring participation by all racial, ethnic, and economic groups. We strongly encourage the Federal government to invest in a nationwide public education campaign regarding the importance of biospecimens in medical research. This could be accomplished by giving small grants to select institutions across the nation, or more simply by adding funds specifically for this type of education to all funded cancer centers and research institutions in the US. If the public is as educated about biospecimens as they are about organ donation, it will be far easier for institutions to obtain informed consent.

ELEMENTS OF INFORMED CONSENT

As mentioned above, pathologists generally do not have contact with the patients who provide their biospecimens and therefore we would defer on the optimal methods of providing consent to those who regularly interface with patients. However, the CAP believes any informed consent process should always include the ten elements below.

1. The specific biospecimen(s) to be donated, or a general reference to the biospecimens from an identified procedure;
2. The uses that might be made of the donated biospecimen, including the primary (intended) use, possible secondary uses, and any limitations on use;
3. Any substantial risks to the donor associated with the donation;
4. The fact that a potential donor who does not give consent will not suffer adverse consequences;
5. The fact that neither the donor nor the donor's family will have any claim to the results of research or to products which may result from use of the biospecimen, or a statement of the rights that the donor or family will have in the results of any research or in any resulting products;
6. The fact that the pathologist and/or laboratory may be compensated for the costs of procuring, storing, processing, and distributing the biospecimen (if such is in fact the case);
7. The policy on disclosure to the patient or family of any information that is learned from review of the biospecimen;
8. The policy on protecting the privacy interests of the patient;
9. The manner and duration of storage, including, where applicable, a statement to the effect that the biospecimen may be retained indefinitely as part of a biorepository; and
10. Possible methods of disposition of the biospecimen (including incineration).

Today, the CAP advocates that informed consent documents reference all additional possible foreseeable uses for the biospecimens including research. We believe "disclosure should be made in a manner that is understandable to a reasonable lay person" and "in the case of a biospecimen donation specifically made for research purposes," that the informed consent document should "cover the following topics: the intended procedures and uses of the biospecimens in the context of the protocol; and the policy governing handling of the discovery of unanticipated clinical information about the donor secondary to the processing of material for the protocol. Further, if the biospecimen is donated for use by a specific researcher or at a specific institution, the consent form should address ownership of the biospecimen." Lastly, any tissue that may end up being "excess" and used for research purposes should be embargoed and "remain available to be returned for additional diagnostic evaluation if necessary. If any excised tissue may be used for research after a diagnosis is reached, the pathologists should make sure that the informed consent form grants permission for this use."

CONCLUSION

The CAP appreciates this opportunity to provide comment on this proposed rule. We support your efforts to update this regulation and support many of the practical goals of this proposal. There remain, however,

significant areas of concern that we hope will be resolved before the NPRM is ready to be finalized. Recently, Secretary's Advisory Committee on Human Research Protections (SACHRP) recommended that:

- The HHS should conduct a comprehensive re-write of the NPRM through a concerted effort to simplify the proposed changes and to focus efforts on selected issues for which there is broad support by the public, investigators, institutional review board professionals, and other experts.
- Prior to publication of final rules, HHS should issue a second NPRM that presents a simplified, focused set of proposals for further public consideration and comment.

We echo SACHRP recommendations to the Secretary that calls for OHRP to consider releasing a revised, simplified set of proposals for notice and comment before finalizing any changes to the Common Rule.

Thank you for your serious consideration for revisions in this memorandum as we all strive to provide the best care for our patients. Please feel free to contact Helena Duncan, CAP Assistant Director, Economic and Regulatory Affairs at hduncan@cap.org if you have any questions on these comments.