



**Re: Federal Policy for the Protection of Human Subjects
Federal Register Vol. 80, No. 173, September 8, 2015**

As an institution dedicated to meeting critical challenges in biomedicine through collaborative, cutting-edge research across disciplines and organizations, the Broad Institute of Harvard and MIT welcomes the opportunity to comment on the proposed revisions to the Common Rule. The Broad Institute applauds OHRP's efforts to modernize and strengthen Federal policy governing research protections and respectfully offers the following comments and observations with regard to the Notice of Proposed Rulemaking (NPRM).

1. Proposed regulatory framework for biospecimens

As one of the leading research institutes engaged in genomic research (including having one of the world's largest sequencing centers), the Broad Institute is well positioned to comment on the NPRM's proposed framework for regulating the use of biospecimens in research. (Additional background on the Broad Institute is provided in the Appendix.)

The stated goal of the NPRM's framework concerning secondary use of biospecimens is to maximize the societal value of research in genomics and other "-omics", while addressing two key ethical concerns:

(i) Participant privacy. The NPRM notes that genomics and related research can generate information that is unique to individuals or to well-defined populations, and that this information can be combined with other data in ways that could result in identification.

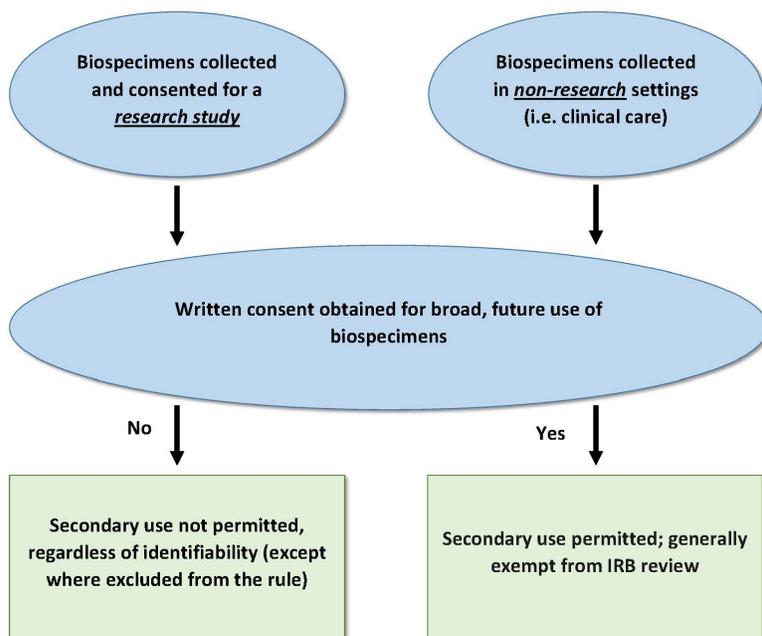
(ii) Participant autonomy. The NPRM also notes that, separate from the issue of privacy, many people wish to have some degree of control over the future use of their biospecimens.

The Broad Institute agrees that both privacy and autonomy are important considerations for regulating the use of biospecimens in a way that maintains public trust in the research enterprise.

The NPRM seeks to facilitate research while addressing these concerns by generally requiring written consent for broad future use of biospecimens in research and, where such consent is given, permitting secondary uses of the biospecimens without further IRB review.

As stated, the NPRM's framework applies to biospecimens collected in both research settings and non-research settings (i.e., clinical care) (Figure 1).

Figure 1. NPRM Proposal for Regulating Use of Biospecimens



The Broad Institute supports the concept, outlined in the NPRM, of obtaining broad consent for future use of biospecimens in a research setting.

The Broad Institute is the largest depositor of genomic data to the National Center for Biotechnology Information's dbGaP repository (Database of Genotypes and Phenotypes), which has required explicit consent for data sharing obtained from biospecimens collected after January 25, 2015. Many investigators are increasingly requesting broad consent for future use of biospecimens or data derived from specimens in research regardless of funding—a practice we highly encourage. Obtaining prospective consent for future use of specimens facilitates broad sharing and use of specimens in research, while also providing individuals the opportunity to give (or withhold) their express permission for those uses. The creation of uniform standards with respect to broad consent would greatly assist investigators in making these requests and would address a growing concern that inconsistencies in consent forms used from one institution to the next could hinder future data sharing efforts.

At the same time, many healthcare providers have expressed concern that a requirement to obtain broad consent for biospecimens obtained in a non-research setting—that is, in the course of healthcare—is impractical and untenable.

They note that a considerable amount of research currently occurs on biospecimens obtained in healthcare settings (and especially in teaching hospitals) that poses very low risks to the research subject. Specifically, the risk of re-

identification is low, while the potential reward of this research is immeasurable. (Examples include: tissue degradation measurements, blood chemistry analyses, urine glucose tests, and heavy metal screening.)

Healthcare providers have expressed concern that requiring written consent for such uses would undermine these research activities, primarily because the costs of obtaining separate, written consent for future uses of biospecimens in the course of healthcare would be so burdensome that many institutions would refrain from making these requests.

The Broad Institute believes these concerns can be addressed by modifying the NPRM to take into account the differences between samples collected initially in the context of research and those that are collected in the context of routine clinical care.

In particular, we suggest the following:

(i) Where specimens are initially collected in a **research** setting (i.e., for a research study), written consent should continue to be required, and secondary uses should require written consent for broad future use, as laid out in the NPRM.

(ii) Where specimens are initially collected in **non-research** settings (i.e., clinical care), the healthcare provider (a) must provide all participants—as part of the standard clinical consent process—the opportunity to “opt out” of all research, and (b) may also choose to request that participants provide broad, written consent for research uses of specimens (as in the research setting).

- Where individuals choose to opt out of all research, their specimens will not be use for any research purposes.

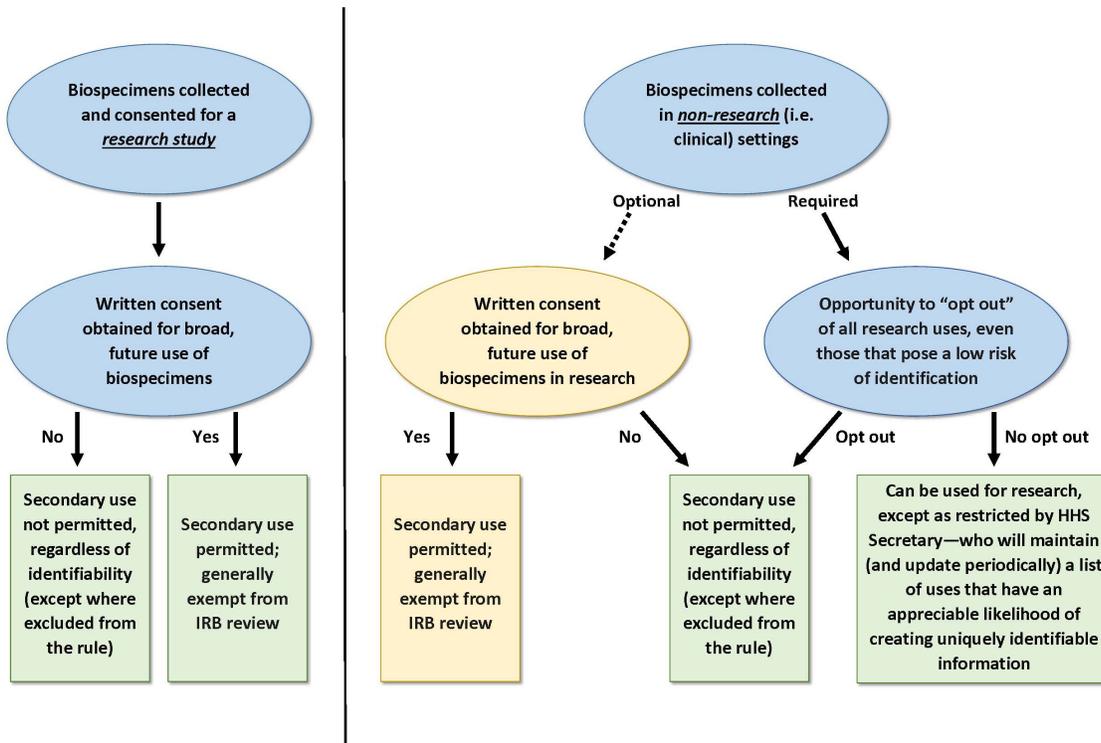
- Where individuals do not choose to opt out of all research but where broad consent has not been obtained, their specimens may be used for “limited research use”—specifically, for research uses that do not have an appreciable likelihood of creating uniquely identifiable information. The HHS Secretary would maintain and update periodically a list of “excluded uses” that are not permitted under limited research use, because they have an appreciable likelihood of creating uniquely identifiable information. Examples might include at least whole genome and whole exome sequencing, and perhaps other forms of “-omics” research.

- Where individuals provide broad consent for research, their specimens may be used in the research setting.

This framework is illustrated in Figure 2.

As compared with the current proposal in the NPRM, this approach has the benefit of (a) reducing the burdens to healthcare providers in the context of clinical care, while (b) respecting personal autonomy by providing individuals the opportunity to opt out of all research and (c) minimizing the risk of identifiability. Importantly, much critical and low-risk research on discarded clinical samples would likely continue unimpeded. Those institutions that wish to perform research with an appreciable likelihood of creating uniquely identifiable information may do so by collecting broad consent.

Figure 2. Alternative Proposal for Regulating Use of Biospecimens



2. Other concerns

- **It is essential that the broad consent template be issued with the final rule.** Delays would inevitably result in confusion and research disruptions.
- **The rule seems to focus on protection of the physical specimen but not the data resulting from the sample.** For example, a patient might undergo whole genome sequencing as part of clinical cancer care, have that sequence data entered into the medical record, then later have the medical record be “de-identified” and sequence data used without consent. This seems contrary to the general principle of autonomy that the rule seeks to protect. The final rule should be clear that the sample and the data are afforded the same protection.

We thank OHRP for its extensive efforts in preparing the NPRM.

Appendix: Background on The Broad Institute of Harvard and MIT

The Eli and Edythe L. Broad Institute of MIT and Harvard was launched in 2004 to empower this generation of scientists to transform medicine by using systematic approaches in the biological sciences to dramatically accelerate the understanding and treatment of disease. The Broad Institute seeks to describe all the molecular components of life and their connections; discover the molecular basis of major human diseases; develop effective new approaches to diagnostics and therapeutics; and disseminate discoveries, tools, methods and data openly to the entire scientific community. The Broad Institute includes faculty, professional staff and students from throughout the MIT and Harvard biomedical research communities and beyond, with collaborations spanning over a hundred private and public institutions in more than 40 countries worldwide.

The vast majority of research carried out at the Broad involves the sharing and use of human biospecimens or genomic data generated from human biospecimens. Last year, more than 25,000 genomes were sequenced at the Broad, and this number is expected to double in the coming year. The Broad has been the leading contributor to The Cancer Genome Atlas (TCGA) and the 1,000 Genomes Project. This year, the Broad was named by NCI as one of two national data-production centers for a five-year project to characterize the genomic changes found in tumors. The Broad has also served as a flagship center for the genetic and molecular analysis of numerous common diseases including type 2 diabetes, heart disease, inflammatory bowel disease, autism, schizophrenia, and bipolar disorder.