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Biobanking, Consent, and Certificates of Confidentiality: Does the ANPRM Muddy the Water?

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Précis

In its Advanced Notice of Proposed Rule Making (ANPRM), the US Department of Health and Human Services proposed substantial changes to how biospecimen research is treated under the regulations governing human subjects research. Currently, much of this research can be conducted without consent because it may not be considered “human subjects” research, is considered exempt, or consent may be waived. Responding to criticisms that scientific changes have made biospecimen research riskier than contemplated when the Common Rule was last amended, the ANPRM proposes to require written consent for biospecimen research, even if they have been stripped of identifiers or initially collected for a non-research purpose.

The ANPRM’s recognition of these risks is consistent with relatively recent NIH recommendations that research projects involving genetics, genomics, or biospecimen repositories should consider getting a Certificate of Confidentiality to provide additional protections to participants where breach of confidentiality is typically the primary risk. Ironically, the ANPRM proposals may make it more difficult to provide these protections. Our paper explores the implications of the conflicting requirements of the Certificate and the ANPRM proposals and makes recommendations for achieving the dual goals of appropriate consent and adequate confidentiality protections.

The U.S. Department of Health and Human Services (HHS) has proposed substantial changes to the current regulatory system governing human subjects research in its Advanced Notice of Proposed Rulemaking (ANPRM), entitled “Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators.”¹ Some of the most significant proposed changes concern the use of biospecimens in research. Because research involving biological materials begins with an initial interaction with an individual, such research falls squarely within the human subjects research regulatory framework known as the “Common Rule,” which applies to research conducted or funded by the HHS and the other signatory agencies and departments.² However, as described in detail below, much biospecimen research may fall within exemptions and exceptions under the Common Rule and, thus, may be conducted without consent. The ANPRM proposes requiring written consent for research use of biospecimens, even if the biospecimens were initially collected for a purpose other than research or have been stripped of identifiers.³

This ANPRM proposal responds to criticisms that the Common Rule does not take into account advances in science that result in projects involving genetics, genomics, or other use of biospecimens, all of which present risks not contemplated at the time the Common Rule was last amended.⁴ The ANPRM argues that, because of the inherent identifiability of biospecimens from which DNA can be extracted, consent should be required for such research.⁵ This proposed change would allow participants to choose whether their biological materials are used in research and some limited control over specific research uses.⁶ Breach of confidentiality is widely recognized as the primary risk of biospecimen research;⁷ for example, research linking individuals or groups to stigmatizing conditions can give rise to psychosocial or even economic harm.⁸ Moreover, study participants are mainly concerned about confidentiality in this context.⁹ The ANPRM addresses the informational risks that accompany biospecimen research primarily through standardized data security measures.¹⁰ Another strategy for addressing informational risks is a Certificate of Confidentiality (Certificate), which protects against compelled disclosure of participant names and other identifying characteristics.¹¹ While, as the ANPRM notes, there are limits to a Certificate's protections and it is no substitute for appropriate data security measures, the National Institutes of Health (NIH), among others, has recommended that research projects involving genetics, genomics, or development of biospecimen repositories consider obtaining a Certificate of Confidentiality (Certificate) to provide additional protections to participants.¹²

Ironically, while the ANPRM seeks to enhance protections to participants in biospecimen research, its consent proposals may make it more difficult to obtain a Certificate and, thus, the additional confidentiality protections recommended for participants in such research. The ANPRM contemplates a brief consent form that would collect all biospecimens relating to interactions with an institution. Thus, the materials may be obtained outside of the research setting, e.g., if biospecimens are collected for clinical purposes, and collected on an institution-wide basis, rather than for a specific research project or even a specific repository.¹³ However, Certificates are only available for research projects and require specific disclosures to research participants.¹⁴ Thus, the ANPRM may prevent researchers from using one of the tools that addresses one of the main concerns – breach of confidentiality – that participants have about participation in biospecimen research. In this article, we explore the implications of these potentially conflicting requirements and make recommendations for revising the regulations to achieve the dual goals of adequate informed consent and confidentiality protections. In doing so, we will draw on previous empirical and analytical work on biospecimen research and our recent empirical work on understanding and usage of Certificates.

Basic Requirements Under the Common Rule

The Common Rule defines “research” as “a systematic investigation...designed to develop or contribute to generalizable knowledge.”¹⁵ All research involving the use of human subjects is subject to the federal regulations.¹⁶ A “human subject” is defined as “a living individual about whom an investigator (whether professional or student) conducting research obtains (1) [d]ata through intervention or interaction with the individual, or (2) [i]dentifiable private information.”¹⁷ All studies involving human subjects (and subject to the Common Rule) must undergo Institutional Review Board (IRB) review and approval.¹⁸

Most importantly, researchers must obtain each subject's consent to participate before the study begins.¹⁹ Informed consent means that the following information must be provided: (1) a statement describing the procedures and purposes of the study "and the expected duration of the subject's participation in the study"; (2) a description of the reasonably foreseeable risks of participation; (3) a description of any reasonably expected benefits to the participants or to others; (4) disclosure of potential alternative procedures or available treatments; (5) "[a] statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained"; (6) contact information for questions related to the research; and (7) a statement that participation is voluntary.²⁰

Exceptions to the Consent Requirement

Despite the mandated protections for informed consent set forth by the Common Rule, much research involving human biological materials may be undertaken without the knowledge or consent of the individuals who donated the materials. When tissue samples are obtained from living individuals for research purposes, such collection is clearly human subjects research because it involves an "intervention or interaction with" a living individual. Guidance from the OHRP makes clear that "*obtaining* identifiable private information or identifiable specimens for research purposes constitutes human subjects research."²¹ Information or specimens are considered "individually identifiable...when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems."²²

However, research involving only coded specimens²³ is not considered human subjects research if:

1. the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
2. the investigators(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
 - a. the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);
 - b. there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
 - c. there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.²⁴

Referred to as the "honest broker" agreement, example (a) involves one investigator sharing specimens she has already collected with another investigator. The second investigator does not obtain the specimens through interaction or intervention with the specimen donors and

does not have access to personally identifiable information about the donors. Such research does not qualify as “human subjects research.” Example (b) involves the use of a central repository that houses biological materials and ensures that such materials are maintained in conformance with the regulatory requirements, including agreements that prohibit release of identifiable information. Because investigators do not have access to any identifiable information of donors, the use of repository materials is not considered “human subjects research.”

The Common Rule also contains exemptions for certain types of research, even though such research may qualify as human subjects research. For example, “[r]esearch involving the collection or study of existing ... pathological specimens, or diagnostic specimens” may be exempt from the Common Rule if the “sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.”²⁵ Under these circumstances, researchers may fall within the exemption by taking steps to avoid having identifiers, by recording information without the identifiers, or by stripping identifiers from the sample. Additionally, the language of the exemption refers to “pathological specimens” or “diagnostic specimens,”²⁶ thus contemplating the possibility that materials collected for clinical purposes may be used for research, but may also fall outside of the protections governing human subjects research.

All of these exceptions involve the secondary use of the specimens, assuming that the specimens were originally collected for some purpose other than the current research. Thus, this secondary use does not involve an interaction or intervention with a living subject that would classify the research as human subjects research and place it within the scope of the federal research regulations.

Lastly, even research involving human subjects that does not fall within the above exemptions may be conducted without the subject’s informed consent if the IRB finds that the research study meets certain criteria. The regulations explain that consent for research may be waived if:

1. The research involves no more than minimal risk to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The research could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.²⁷

Thus, a researcher may seek to conduct research under a waiver of consent when she desires to use the specimens for a secondary purpose not addressed when the donor consented to the donation. Because the materials have already been collected from the living individual, no additional physical risk to subjects would exist. Though confidentiality and identification risks must be considered, the researcher may state that the risk of identification is extremely low, as she does not have access to any of the identifiers linked to the donors. Finally, if the researcher requires a very large number of specimens that were collected over time, she

could show that the research study would not be “practicable” without the waiver because it may be impossible for her to obtain consent from each donor.

History and Purpose of Certificates of Confidentiality

Originally established by Congress in 1970 as part of the war on drugs, Certificates allows researchers to refuse to provide the names and other identifying characteristics of their research participants to officials in any “Federal, State, or local civil, criminal, administrative, legislative, or other proceedings.”²⁸ Because prior research concerning drug use engendered arrests of both researchers and research participants,²⁹ lawmakers created the Certificate as a mechanism to assure drug-using research participants in drug abuse and addiction studies that their identities would remain strictly confidential.³⁰ Over time, Congress expanded the scope of Certificates to other research contexts dealing with sensitive information more generally. The current authorizing statute provides:

“The Secretary may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals.”³¹

NIH, one of the federal entities that issues Certificates, has further explained that Certificates may be appropriate and granted for studies “collecting information that if disclosed could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.”³²

Thus, the purpose underlying Certificates is the desire “to reduce impediments to biomedical/bio-behavioral research subject recruitment.”³³ Despite this singular goal, Certificates do not forbid or protect against all forms of disclosure of research participant identities.³⁴ Permissible disclosures include voluntary disclosures by research participants themselves and disclosures by investigators in situations of child abuse, threat of harm to self or others, or reportable communicable disease.³⁵ Therefore, each investigator must balance the protections afforded by a Certificate with the need for voluntary and other permissible disclosures when crafting informed consent language that accurately describes the Certificates’ protections.

Though the strengths of the protections afforded by a Certificate have not been regularly tested in court, a case from the Court of Appeals of New York, *People v. Newman*, is frequently cited in support of the Certificates’ protections.³⁶ In *Newman*, the Director of the New York City Methadone Maintenance Treatment Program refused to provide the local district attorney with the photographs of the individuals in the treatment program, asserting complete protection from such a subpoena because the program had been issued a Certificate.³⁷ Even though the prosecutor subpoenaed the photographs in conjunction with a

murder investigation, the court determined that the Director of the methadone clinic could neither be compelled to produce the photographs of the study participants, nor be held in contempt for failing to do so,³⁸ reasoning that “[t]he authority in the 1970 Act to grant absolute confidentiality was designed to help ensure the success of drug research programs in which addict participants require anonymity.”³⁹ However, despite the outcome of this case, some have argued that its precedential value is limited because the Court primarily focused on resolving a dispute between two related statutes, rather than on the Certificate itself.⁴⁰

Obtaining and Using a Certificate of Confidentiality

Any investigator may apply for a Certificate from NIH,⁴¹ even if the project is not federally funded.⁴² Each Certificate is specific to the research project, and a Certificate will only be given for a single, well-defined project.⁴³ Prior to applying for a Certificate, a researcher must first obtain approval from an Institutional Review Board (IRB).⁴⁴ The application for the Certificate must contain the start date and expected end date of the project.⁴⁵ The Certificate protects from compelled disclosure the personally identifiable information of any individual who participates as a research subject during the period of time the Certificate is in effect.⁴⁶ Even after the project itself has ended, the protection provided by the Certificate for the participants remains permanently.⁴⁷

The application for the Certificate must also contain a description of the aims and research methods of the project, particularly the procedures to be used in collecting and storing the identifying information of the research participants.⁴⁸ This section of the application should contain information about the potential research participants, including the “number of subjects to be included in the study, the source from which they will be recruited, and a description of the study population (e.g., gender, age, race, etc.).”⁴⁹ The application must describe the ways in which the research participants’ identities will be protected.⁵⁰ NIH provides suggestions for protecting subjects’ identities, such as coding the subjects by numbers and not by names, maintaining identifying information in locked files, and destroying all identifiers when the study is completed.⁵¹ Additionally, the application must include the reasons why the investigator needs the protection of a Certificate and a description of the sensitive material and identifying information that the investigator will collect.⁵²

Lastly, the researcher must include the informed consent form to be signed by the research participants, as approved by the IRB.⁵³ The informed consent form should not only explain the protections given to participants by the Certificate, but also caution participants that their participation in the study will not be protected if they or one of their family members voluntarily discloses their participation.⁵⁴ The form must detail the situations in which the investigator plans to voluntarily disclose identifying information about research participants, for example, in situations such as suspected child abuse or harm to self or others.⁵⁵

Certificates of Confidentiality and Biospecimen Repositories

For the past 100 years, research institutions in the United States have collected and stored human tissues.⁵⁶ In 1997, the Office for Protection from Research Risks (OPRR), (the

predecessor to the Office for Human Research Protections (OHRP)), issued guidance for human biospecimen repositories sponsored by HHS.⁵⁷ Explaining that “Human Tissue Repositories collect, store, and distribute human tissues for research purposes,” OPRR broke down the use of such repositories into three categories: (1) the **collectors** of tissue samples; (2) the **repository** storage and data management center; and (3) the **recipient** investigators.⁵⁸ Each of these stages requires distinct procedures to protect the human subjects involved. While IRB approval and informed consent are necessary at both the collection and data management stages, OPRR specifically recommended that a “Certificate ... be obtained to protect the confidentiality of repository specimens and data.”⁵⁹ The NIH guidance on Certificates echoes these recommendations, listing “genetic studies, including those that collect and store biological samples for future use” among its “examples of research projects that are eligible for a Certificate.”⁶⁰ Similarly, the National Cancer Institute has recommended Certificates for at least some biorepositories.⁶¹

Despite these recommendations for Certificate use for biorepositories, a 2003 study of twelve major U.S. repositories reported that only one had obtained a Certificate.⁶² A subsequent study concerning the best practices in maintaining a repository, including consent and confidentiality considerations, is utterly void of any discussion about obtaining Certificates.⁶³ Finally, our recent study of IRB Chairs’ use and understanding of Certificates found that only about one-quarter of IRBs would require or recommend a Certificate for biobanks.⁶⁴ However, as the NIH has suggested, it is possible that biological materials could be relevant in litigation. For example, several unreported cases we found involved demands for research data and information connected to litigation over exposures to medications or chemicals.⁶⁵ In addition, counsel indicated cases sometimes involved domestic disputes, such as divorce and custody matters.⁶⁶ Stored materials could be useful evidence in such instances.

Advanced Notice of Proposed Rule Making: Changes to Consent of Biospecimen Collection

As discussed above, there are many instances under the Common Rule in which a donor’s consent is not required to biospecimen research or for secondary research use of identifiable data. However, the ANPRM, issued by HHS in July of 2011, seeks to address some of the gaps in consent created by the current regulations.⁶⁷

The primary change the ANPRM proposes is requiring biospecimen donors “to give consent, in writing, for research use of their biospecimens.”⁶⁸ Regarding researcher use of pre-existing data,⁶⁹ “if the data was originally collected for *non-research* purposes, then... written consent would only be required if the researcher obtains information that identifies the subjects.”⁷⁰ However, if such pre-existing data was obtained for *research purposes*, “then consent would be required *regardless* of whether the researcher obtains identifiers.”⁷¹ Though subtle, this proposed change to the Common Rule nullifies “the allowable current practice of telling the subjects, during the initial consent, that the data they are providing will be used for one purpose, and then after stripping identifiers, allowing it to be used for a new purpose to which the subjects never consented.”⁷²

Although the proposed change appears to place greater restrictions on the secondary use of existing biospecimens, the ANPRM reasons that the necessary consent requirements will be met at the time the specimens are originally collected through the use of a “standard, brief general consent form allowing for broad, future research.”⁷³ The common form would allow consent to be granted for all research going forward. Instead of requiring project-specific consent forms to be signed by participant donors, the ANPRM suggests that the consent “be broad enough to cover all data and biospecimens to be collected related to a particular set of encounters with an institution (e.g., hospitalization) or to any data or biospecimens to be collected at anytime by the institution.”⁷⁴ It is important to note that the proposed general consent form would “permit the subject to say no to all future research.”⁷⁵ Additionally, subjects would be offered the opportunity to express preferences regarding “a handful of special categories of research with biospecimens that, given the unique concerns they might raise for a significant segment of the public, [which] would be dealt with by check-off boxes allowing subjects to separately say yes or no to that particular type of research (e.g., perhaps creating a cell line, or reproductive research).”⁷⁶

The ANPRM not only proposes a common and general consent form, but also a simplified one. This proposal is consistent with its other recommendations with respect to consent generally. Various aspects of consent forms have been criticized, including the length of time IRBs spend editing and revising consent forms, the length of forms, the use of complex legal language, and the failure to include important pieces of information needed by participants to make intelligent decisions.⁷⁷ In response to these criticisms, the ANPRM proposes a number of changes to informed consent requirements, including:

1. prescribing appropriate content that must be included in consent forms, with greater specificity than is provided in the current regulations;
2. restricting content that would be inappropriate to include in consent forms;
3. limiting the acceptable length of various sections of a consent form;
4. prescribing how information should be presented in consent forms, such as information that should be included at the very beginning of the consent form, or types of information that should be included in appendices and not in the main body of the consent form;
5. reducing institutional “boilerplate” on consent forms (that is, standard language that does little to genuinely inform subjects, and often is intended to primarily protect institutions from lawsuits); and
6. making available standardized consent form templates, the use of which could satisfy applicable regulatory provisions.⁷⁸

As a result of these recommendations, the actual language of an informed consent form will be set forth in the regulations outside of IRB drafting, just as the granting of general consent for research involving biological materials will be available outside of project-specific purposes and IRB review. The overall goal is to have consent forms that are shorter, more readily understood, less confusing, that contain all key information, and that can serve as an

aid to help someone make an informed decision about whether to participate in a particular study.

Advanced Notice of Proposed Rule Making: Guarding against Informational Risks Posed by Identifiable Data

The ANPRM takes into account the information risks that come from both primary and secondary research use of identifiable data.⁷⁹ As the ANPRM explains, these risks arise because “what constitutes ‘identifiable’ and ‘de-identifiable’ data is fluid,” particularly in an era of rapid technological advances and increasingly accessible data that may “allow identification of an individual from data that is currently de-identified.”⁸⁰ Given the inherent identifiability of DNA, this is especially true in the area of biological materials.⁸¹

Indicating that “IRB review ... may not be the best way to minimize the informational risks associated with data on human subjects,”⁸² the ANPRM proposes three requirements to strengthen protections for research that pose informational risks. First, the ANPRM suggests modeling research data security standards on the HIPAA security rule, including use of data encryption, strong physical safeguards, access controls, and audit trails.⁸³ Second, the proposed changes would permit data to be considered a de-identified or limited data set, under the HIPAA model, when investigators have access to identifiers, but do not record them. Part of the rationale for this proposal is to avoid the need for researchers to engage “honest brokers” to deidentify data.⁸⁴ Third, the ANPRM proposes “periodic random retrospective audits” to ensure enforcement under the Common Rule.⁸⁵

From the new consent requirements for secondary uses of biospecimens and for research projects in general, to the suggestions for heightened data security and protection, the ANPRM reflects the recognition that changes in the field of genomics have dramatically increased the amount and nature of information about individuals that can be obtained from their DNA. The ANPRM posits that while “[a]n accumulating body of data indicates that... most individuals want to be able to decide whether their biospecimens are available for research, they often do not desire to have control over which specific researchers use their samples, for which diseases, at which institutions.”⁸⁶ Its solution is a generalized informed consent that is simplified for easier use by all subjects.⁸⁷

Use of Certificates of Confidentiality for Biospecimen Research

The ANPRM proposals regarding biospecimen research recognize the increasing identifiability of biospecimens due to scientific advances and increasing development of DNA databases. As mentioned previously, in such research studies, breach of confidentiality is not only typically the primary risk, but also the main concern of study participants.⁸⁸ This recognition of the informational risks of biospecimen research is consistent with relatively recent recommendations from NIH that research projects involving genetics, genomics, or the development of biospecimen repositories consider obtaining a Certificate to provide additional protections to donors or research participants.⁸⁹ Specifically, the National Cancer Institute (“NCI”) suggests that “Certificates ... should be considered by the biospecimen resource and/or the recipient investigator depending on the level of privacy protection

indicated by the study design.”⁹⁰ Once a Certificate has been obtained, the biospecimen resource must ensure that the existence and use of the Certificate is “explicitly stated in the informed consent document,”⁹¹ making donors aware of the heightened protections surrounding the biorepository.

Further, NIH acknowledged that repositories may become targets of law enforcement officers seeking to access de-identified genotype and phenotype data to search for matches with DNA specimens collected for forensic purposes.⁹² While “NIH acknowledges that legitimate requests for access to data made by law enforcement offices to the NIH may be fulfilled,” it warns repositories that this may result in law enforcement officers seeking to compel disclosure of identifying information connected to the DNA data given to researchers and institutions for studies.⁹³ To protect the confidentiality of identifying information, “NIH explicitly encourages investigators to consider the potential appropriateness of obtaining a Certificate as an added measure of protection against future compelled disclosure of identities for studies planning to collect genome-wide association data.”⁹⁴ The NIH has not altered its recommendations for repositories to consider Certificates despite the enactment of the Genetic Information Nondiscrimination Act (GINA).⁹⁵ Although GINA provide protections against discrimination on the basis of genetic information, its protections only extend to employment and health insurance decisions and does not apply to employers with less than 15 employees.⁹⁶ It does not apply to a number of other contexts, such as life, disability, and long-term care insurance or education. Nor does it apply to all health information, including information that could be obtained from biospecimens.⁹⁷ Thus, its enactment does not eliminate all confidentiality concerns nor the need for a Certificate as only a Certificate can protect a participant’s identity from discovery, rather than forbid discrimination once the identity is uncovered as required by GINA.

NIH also recognizes that emerging technologies have made re-identifying genetic data easier over time and that data that was once considered “de-identified” can no longer be labeled as such.⁹⁸ Some studies, for example, have shown that researchers can identify an individual with only seventy-five nucleotide polymorphisms (SNPs) from that person.⁹⁹ Other studies have conveyed a statistical method for determining individual genotypes within a mix of DNA samples or datasets containing aggregate SNPs.¹⁰⁰ Reidentification from a SNP collection requires an identified sample or “reference sample.”¹⁰¹ As the use of repositories expands and DNA databases proliferate (e.g., CODIS), reference samples will become more available and reidentification more likely. There is limited information about how often research data is subpoenaed, although our research suggests they are relatively rare.¹⁰² Moreover, specimens may be more readily available from other sources. Nevertheless, researchers have an obligation to protect the confidentiality of participants, who contribute specimens to benefit others, not themselves and to maintain public trust in the research enterprise.¹⁰³ Obtaining a Certificate for repositories is a simple way to add an extra layer of protection for donors’.

The ANPRM acknowledges Certificates as a confidentiality tool, although does not endorse them. Instead, the ANPRM notes Certificates’ limitations – that they do not *require* investigators to refuse to disclose identifying information nor do they protect against

unauthorized or accidental disclosures because of inadequate data security procedures.¹⁰⁴ Nevertheless, Certificates are recognized as an important tool that supplements, not supplants, other confidentiality protections.¹⁰⁵ Our recent research suggests that, despite uncertainty about their effectiveness, Certificates often are effective in protecting identifiable data.¹⁰⁶

Disconnect Between the ANPRM and the Use of Certificates of Confidentiality

The changes proposed in the ANPRM seek to address many of the same risks that are covered by Certificates, but ironically, the ANPRM recommendations may make it more difficult to provide protections to research participants. By encouraging a general consent form for biospecimen research and placing the informed consent form for such research and the handling of informational risks outside of IRB review, the ANPRM makes it difficult, if not impossible, for researchers to comply with the requirements for obtaining a Certificate for their study. As a result, the study is cut off from protections widely recommended for these studies.

As described above, a Certificate is available for a “single, well-defined” research study. Accordingly, a Certificate may not be available to cover the myriad of research projects that could fall under the broad general consent proposed by the ANPRM. This is perhaps especially true when biospecimens are collected in connection with an “encounter with an institution (e.g., hospitalization),”¹⁰⁷ and where the connection to research is tenuous. Certificates originated to protect study participants, not patients.¹⁰⁸ Given that repositories have received Certificates for broad research goals by treating the repository as the single, well-defined research project, perhaps the repository may be able to be structured to meet this particular requirement.

The problem arising from the ANPRM proposals may be more difficult to overcome. To obtain a Certificate, a researcher must draft an informed consent form for the project that not only explains that a Certificate will be used in protecting the identities of the research participants, but also warns participants of the consequences of voluntary disclosure of their research participation. The informed consent form must be tailored to the research project’s aims and risks so that participants are fully aware of the necessity for protection of identity and rely upon these considerations in choosing to participate.

These requirements vary greatly from the informed consent proposals contained in the ANPRM. Instead of requiring individual drafting by the researcher and subsequent approval by an IRB, the ANPRM proposes a standard, brief informed consent form allowing for all types of future research to be conducted with a research participant’s tissue. These consent forms will not contain any discussion of specific research project’s use of the biospecimens collected.¹⁰⁹ Under the ANPRM, unless all repositories are required to have a Certificate, the required language is unlikely to be included in the consent form, and certainly not in the same detail as currently contemplated by the Certificate application requirements. Moreover, even if a version of the standardized consent form does include the required Certificate language, doing so may conflict with the ANPRM goals of shortening and simplifying

consent. Empirical studies have suggested that the NIH-recommended Certificate language can be confusing to participants,¹¹⁰ and that including Certificate language can increase time needed to obtain consent.¹¹¹ Finally, the proposed ANPRM consent forms will not have the IRB stamp of approval, which creates another barrier to obtaining a Certificate.¹¹²

The ANPRM also seeks to move the handling of informational risk connected with repository studies outside the IRB process. In conjunction with NIH and several recent studies, the ANPRM acknowledges that informational risks stem from the fact that data that was previously considered de-identified can now be reidentified through emerging technologies.¹¹³ As a result, the ANPRM suggests that the protection of identifying information be removed from IRB oversight and instead regulated through data security standards. Rather than having an IRB evaluate the informational risks of each study and requiring a researcher to propose specific methods for diminishing these risks, as required in order for a study to qualify for a Certificate, the ANPRM proposes broad requirements be used for every study. Such generalized standards will not meet the specifics required to obtain a Certificate. Additionally, because Certificates are research-project specific and managed by the governing IRB, the need for a Certificate to protect against informational risks may not even be raised at the time the project ensues because the ANPRM takes the informational risks out of the IRB's purview. The HIPAA data security model does not include protection against subpoena; indeed, there are numerous exceptions to HIPAA protection.¹¹⁴ Accordingly, this approach leaves projects open to the risk of compelled disclosure of research participants' identities.

Recommendations

Overall, the changes proposed by the ANPRM demonstrate a step in the right direction because the current regulations have gaps that create informational risks and privacy concerns. The ANPRM seeks to address these gaps and ensure that genetic and medical research utilizing biobanks seek permission to store and use biospecimens, appropriately notify study participants of research risks, and protect such participants from harm caused by disclosure or re-identification. However, the proposed changes contained in the ANPRM must be considered in conjunction with the other rules and best practices that have been developed to protect human subjects. In addition, the proposed changes must be closely examined for unintended consequences, such as the conflicts between the ANPRM and the use of Certificates for research projects involving biobanks that we have highlighted here.

In the particular context we have raised, our research suggests that Certificates, combined with other security measures, can be an effective tool for protecting confidentiality.¹¹⁵ Certificates are relatively easy to get¹¹⁶ and address research participants' main concern in biospecimen research. There is little reason *not* to provide this additional layer of protection. Thus, we believe that this conflict between the ANPRM and Certificates should be resolved and explore three different mechanisms for doing so. First, we believe that the conflicts between the ANPRM and Certificates may be resolved, without sacrificing the beneficial aspects of the ANPRM, through changes to the proposed rules. A simplified, standardized consent form could be promulgated as a *model consent form* to be used in biobanking research, rather than a *mandated form*. IRB approval of the project-specific consent form

would still be required—to satisfy the requirements of the Certificate application process—and the form itself would be shorter and more uniform to fulfill the purpose set forth in the ANPRM. The IRB would remain involved in the process: it would review the repository consent form, would still be able to weigh the risks and benefits of recommending a Certificate, and would approve any necessary Certificate language within the consent form. A model biobanking consent form created under the ANPRM should include the recommended NIH Certificate language, at least as an option. Such inclusion would provide a potential mechanism for protecting identifiable data from compelled disclosure, in keeping with the ANPRM's attention to the informational data risks associated with biorepositories.¹¹⁷ This approach would also help address NIH's requirement for a consent form that includes language about the Certificate as part of the application process.

While considering how the Certificate could work within the ANPRM, it would be appropriate to reconsider the recommended consent language about the Certificate. As the ANPRM states, informed consent forms have become highly complex and confusing documents for the majority of study participants,¹¹⁸ and scholars analyzing Certificate language have echoed this sentiment.¹¹⁹ One study on the readability of informed consent language found that a majority of informed consent forms fall in the more difficult, higher grade level category of readability, despite IRBs' desires and attempts to include language at a lower reading level.¹²⁰ Interestingly, institutions that experienced compliance issues resulting in OHRP oversight were more likely to have consent forms that met the desired level of readability, suggesting a positive role for federal involvement.¹²¹ The problem, however, is that the current NIH recommended consent language concerning Certificates scores at a 12th grade reading level.¹²² To put this in perspective, almost half of American adults read at or below an 8th grade reading level.¹²³ Developing standardized and simplified Certificate consent language would aid in easing the tension with the ANPRM and promoting human subjects protection goals.

Alternatively, conflicts between the ANPRM and the use of Certificates for biorepositories may be addressed through changes to the Certificate application process to accommodate the recommendations contained in the ANPRM. Because the relevant parts of the Certificate application process are not governed by 42 U.S.C. § 241(d) or the accompanying regulations, changes to the process may avoid some of the typical administrative hurdles created by the notice and comment period that accompanies formal rulemaking. Instead, NIH may consider an adjustment to the Certificate application process for biorepositories in light of the suggestions and changes proposed by the ANPRM. This adjustment may include acceptance of the standardized informed consent form created by the ANPRM to fulfill the Certificate application requirement, even though the form would be crafted outside the IRB overseeing the repository.

The justification for NIH making such an adjustment to its Certificate application process for biorepositories is two-fold. First, NIH has made clear that “[g]enetic studies, including those that collect and store biological samples for future use” involve sensitive information eligible for Certificate protection.¹²⁴ The increasing ability to reidentify individuals from such specimens only increases the need for greater confidentiality protections of specimen donors. Second, various NIH components have recommended Certificates for

biorepositories, as well as best practices for repositories. In fact, most biorepositories operate under similar practices and procedures (in contrast to the variation among other types of research projects eligible for Certificates). Thus, a process that facilitates obtaining a Certificate and that is consistent with the ANPRM, may make sense in the realm of biorepositories, but not, for example, studies with widely varying procedures and risks, such as HIV prevention studies or drug abuse studies.

We have described some technical changes that might resolve the tensions between the ANPRM and the NIH Certificates application process, but a bolder option is also available. While Certificates are an important tool to protect the confidentiality of sensitive, identifiable data, researchers – particularly those working with biorepositories – may not be aware of their existence.¹²⁵ Indeed, only about one-quarter of IRBs require or recommend Certificates for biobanks, and legal demands for research data may arise unexpectedly and be only tangentially related to the project.¹²⁶

Perhaps the ANPRM provides the opportunity to substitute the piecemeal approach of the Certificate program for a more comprehensive protection against compelled disclosure of research data. Incorporating Certificate-like protections into the general human subjects protections would ensure that such protections are not overlooked and would treat all participants equally with respect to confidentiality. The ethical rationale is simple: Research participants share their information to benefit the rest of us; both the principles of respect for persons and beneficence suggest that their identifying information should not be made available to be used against them. There is legal precedent for protecting research data for entire programs, rather than on a project-by-project basis through Certificates.¹²⁷ Such a move would be controversial and may not be able to be accomplished through the regulatory process alone, but it is worth thinking through how this option could achieve the goals reflected in the ANPRM.

Each of these approaches have pros and cons. There are strong reasons, for example, to extend protections against subpoena to all research data. However, we are cognizant of the legal and political challenges to achieving that goal. Accordingly, while that may serve as a long-term goal, it may be more prudent to start with a short term fix and either amend the ANPRM proposals or the NIH Certificate application process to facilitate use of Certificates for biobanking, as many have recommended.

Conclusion

The advances and proposals contained in the ANPRM are certainly a step in the right direction and should be encouraged. However, using the example of Certificates for biobanking, we have demonstrated that aspects of the ANPRM may clash with other legal requirements or best practices. As we suggest, there are numerous avenues through which such conflicts may be resolved. Any solution, however, requires examining the ANPRM in the broader context of research ethics to ensure that, in the end, changes to the regulatory scheme advance the protection of human subjects.

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References

1. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512 (Jul. 26, 2011) [hereinafter ANPRM] (to be codified at 45 C.F.R. pts. 46, 160, and 164 and 21 C.F.R. pts 50 and 56).
2. The Common Rule is codified at 45 C.F.R. pt. 46, subpart A. Promulgated by HHS, the Rule applies to research conducted by the Department of Agriculture, Department of Energy, National Aeronautics and Space Administration, Department of Commerce, Consumer Product Safety Commission, International Development Cooperation Agency, Agency for International Development, Department of Housing and Urban Development, Department of Justice, Department of Defense, Department of Education, Department of Veterans Affairs, Environmental Protection Agency, National Science Foundation, Department of Transportation, and the Central Intelligence Agency. While the Food and Drug Administration has concurred with the Federal Policy, it has not adopted the policy in its entirety and maintains changes from the policy in its IRB and informed consent regulations. *See* Protection of Human Subjects; Informed Consent; Standards for Institutional Review Boards for Clinical Investigations, 56 Fed. Reg. 28025 (June 18, 1991) (to be codified at 21 C.F.R. pts. 50 and 56).
3. ANPRM, *supra* note 1, at 44519.
4. *See* McGuire, Amy L. Identifiability of DNA Data: The Need for Consistent Federal Policy. *American Journal of Bioethics*. 2008; 8:75–76. [PubMed: 19003718] Wolf, Leslie E. Advancing Research on Stored Biological Materials. *Reconciling Law, Ethics, and Practice*, *Minnesota Journal of Law, Science & Technology*. 2010; 11:99–156.
5. ANPRM, *supra* note 1, at 44519, 44524.
6. ANPRM, *supra* note 1, at 44519–44520. The ANPRM suggests use of check boxes to allow participants to say no to a limited number of types of research that may be objectionable. *Id.*
7. *See, e.g.* Nietfeld JJ, Sugarman Jeremy, Litton Jan-Eric. The Bio-Pin: a concept to improve biobanking. *Nature Reviews Cancer*. 2011; 11:303–308.
8. Wolf, *supra* note 3, at 118–125 (discussing the Havasupai case); U.S. Health and Human Services, Office for Human Research Protections, Guidance on the Genetic Information Nondiscrimination Act: Implication for Investigators and Institutional Review Boards, available at <http://www.hhs.gov/ohrp/policy/gina.html> (March 24, 2009)(last accessed 1/22/13).

9. Potential research participants have identified that their greatest concern, and thereby their main reason for nonparticipation in biospecimen research, relates to the confidentiality of their health-related and genetic information. Katrina A.B. Goddard et al., *Biobank Recruitment: Motivations for Nonparticipation, Biopreservation & Biobanking* 7 (2009): 119–121, at 120 (reporting the most frequent concerns were security and confidentiality of health information (73%) and genetic information (61%)). Further, the enactment of HIPAA demonstrates the heightened concerns surrounding the need to protect health information, including data collected for research purposes. *See generally* Peter M. Currie, *Balancing Privacy Protections with Efficient Research: Institutional Review Boards and the Use of Certificates of Confidentiality*, *IRB Ethics & Hum. Research* 27 (2005): 7–12.
10. ANPRM, *supra* note 1, at 44526.
11. *See infra* discussion of History and Purpose of Certificates of Confidentiality.
12. ANPRM, *supra* note 1, at 44525. Office for Protection from Research Risks, Department of Health and Human Services, *Issues to Consider in the Research Use of Stored Data or Tissues* (1997), <http://www.hhs.gov/ohrp/policy/reposit.html> (last visited Jan. 21, 2012); National Institutes of Health, Department of Health and Human Services, *Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS)*, Aug. 28, 2007, <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html#protection> (last visited Feb. 19, 2012) [hereinafter GWAS].
13. ANPRM, *supra* note 1, at 44519.
14. National Institutes of Health. [last visited Jan. 21, 2012] *Certificates of Confidentiality: Background Information*. 2003 Jul 21. <http://grants.nih.gov/grants/policy/coc/background.htm>
15. 45 C.F.R. § 46.102(d) (2012).
16. 45 C.F.R. § 46.101 (2012).
17. 45 C.F.R. § 46.101(f) (2012). According to the regulations, “[i]ntervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.” 45 C.F.R. § 46.101(f).
18. 45 C.F.R. § 46.101 (2012) (requiring IRB approval for all studies involving human subjects). The regulations further set forth the elements to be reviewed by the IRB in 45 C.F.R. § 46.111: “(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied: (1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes. (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility. (3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by § 46.116. (5) Informed consent will be appropriately documented, in accordance with, and to the extent required by § 46.117. (6) When appropriate, the research plan

makes adequate provision for monitoring the data collected to ensure the safety of subjects. (7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. (b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.”.

19. 45 C.F.R. § 46.111 (2012) (requiring informed consent from research participants).
20. 45 C.F.R. § 46.116 (2012). Although not typically applicable to biospecimen research, the Common Rule also requires “[f]or research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.” *Id.* 46.116(a)(6).
21. Office for Human Research Protections (OHRP). Department of Health and Human Services, Guidance on Research Involving Coded Private Information or Biological Specimens. last visited Feb. 4, 2012 <http://www.hhs.gov/ohrp/policy/cdebiol.html> OHRP further explains that “[o]btaining identifiable private information or identifiable specimens includes, but is not limited to: (1) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to investigators from any source; and (2) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.”.
22. OHRP, *supra* note 51.
23. The OHRP Guidance considers information or specimens “coded” when “(1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.” OHRP, *supra*, note 51.
24. OHRP, *supra*, note 51.
25. 45 C.F.R. § 46.101(b)(4) (2012).
26. 45 C.F.R. § 46.101(b)(4).
27. 45 C.F.R. § 46.116(d)(1)–(4) (2012).
28. 42 U.S.C. § 241(d) (2012). The authorizing statute does not use the phrase “Certificate of Confidentiality.” The term may come from the regulations, which refer to a “Confidentiality Certificate.” 42 C.F.R. § 2a. In any event, the protections afforded by 42 U.S.C. § 241(d) are commonly referred to as a “Certificate of Confidentiality” by NIH and other issuers, IRBs, and the researchers who use them.
29. *See Federal Drug Abuse and Dependence Prevention, Treatment, and Rehabilitation Act of 1970, Part I: Hearings on S. 3562, S. 3246, and S. 2785 Before the Special Subcomm. On Alcohol and Narcotics of the S. Comm. On Labor and Public Welfare*, 91st Cong. (1970).
30. *Federal Drug Abuse and Dependence*, *supra* note 9, at 169.
31. 42 U.S.C. § 241(d) (2012).
32. National Institutes of Health. [last visited Jan. 21, 2012] NIH Announces Statement on Certificates of Confidentiality, NOT-OD-02-037. 2002 Mar 15. <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-037.html>
33. National Institutes of Health. [last visited Jan. 21, 2012] Certificates of Confidentiality: Background Information. 2003 Jul 21. <http://grants.nih.gov/grants/policy/coc/background.htm>
34. National Institutes of Health. [last visited Jan. 21, 2012] Slide Presentation on Certificates of Confidentiality. 2002 May 3. http://grants.nih.gov/grants/policy/coc/slides_020503/index.htm
35. NIH Slide Presentation, *supra* note 34.
36. 32 N.Y.2d 379 (1973). Because such cases involve discovery disputes that rarely give rise to final orders, there are only a few reported cases involving Certificates. In addition to *Newman*, they are: *People v. Still*, 369 N.Y.S.2d 759 (App. Div. 1975) (holding that methadone clinic had to produce clinic documents when the individual to whom the information pertained requested their disclosure to defend against criminal charges) and *North Carolina v. Bradley*, 634 S.E.2d 258 (N.C. Ct. App.

2006) (holding that defendant was not entitled to research records as immaterial to the case, although the records were produced under a protective order for purposes of the appeal). For a further discussion of cases involving Certificates, see Leslie E. Wolf, *et al.*, *Certificates of Confidentiality: Protecting Human Subjects Research Data in Law and Practice*, Minnesota Journal of Law, Science & Technology (*in press*, 2013).

37. 32 N.Y.2d at 382–83.
38. 32 N.Y.2d at 387–90.
39. 32 N.Y.2d at 387.
40. Beskow, Laura M.; Dame, Lauren; Costello, E. Jane Certificates of Confidentiality and Compelled Disclosure of Data. *Science*. 2008; 322:1054–1055. [PubMed: 19008431]
41. Federal agencies other than NIH issue Certificates. These include the Centers for Disease Control and Prevention, the Health Resources and Services Administration, the Indian Health Service, and the Substance Abuse and Mental Health Services Administration, which issues Certificates only for research they fund. The Food and Drug Administration, like the NIH, issues Certificates regardless of federal funding. National Institutes of Health. Frequently Asked Questions: Certificates of Confidentiality. 2011 Jun 20. last visited Mar. 19, 2012 <http://grants.nih.gov/grants/policy/coc/faqs.htm#133> However, we focus on the NIH because most researchers look to the NIH and the NIH has taken a leading role of educating researchers about Certificates through its “kiosk” website.
42. NIH, Slide Presentation, *supra* note 34.
43. NIH, Slide Presentation, *supra* note 34.
44. National Institutes of Health. [last visited Jan. 21, 2012] Detailed Application Instructions for Certificate of Confidentiality: Extramural Research Projects, para. 5(a). 2002 Mar 15. http://grants.nih.gov/grants/policy/coc/appl_extramural.htm
45. NIH, Detailed Application Instructions, *supra* note 44 at para. 7.
46. NIH, Detailed Application Instructions, *supra* note 44 at para. 7.
47. NIH, Detailed Application Instructions, *supra* note 44 at para. 7.
48. NIH, Detailed Application Instructions, *supra* note 44 at para. 8.
49. NIH, Detailed Application Instructions, *supra* note 44 at para. 8.
50. NIH, Detailed Application Instructions, *supra* note 44 at para. 9.
51. NIH, Detailed Application Instructions, *supra* note 44 at para. 9.
52. NIH, Detailed Application Instructions, *supra* note 44 at para. 10.
53. NIH, Detailed Application Instructions, *supra* note 44 at para. 11.
54. NIH, Detailed Application Instructions, *supra* note 44 at para. 11.
55. NIH, Detailed Application Instructions, *supra* note 44 at para. 11.
56. Elisa Eiseman et al., Case Studies of Human Tissue Repositories: “Best Practices” for a Biospecimen Resource for the Genomic and Proteomic Era, at iii (RAND 2003).
57. Office for Protection from Research Risks (OPRR). [last visited Jan. 21, 2012] Department of Health and Human Services, Issues to Consider in the Research Use of Stored Data or Tissues. 1997. <http://www.hhs.gov/ohrp/policy/reposit.html>
58. OPRR, *supra* note 37.
59. OPRR, *supra* note 37.
60. NIH, *supra* note 41, at FAQ C3.
61. National Cancer Institute (NCI). Department of Health and Human Services, Office of Biorepositories and Biospecimen Research. National Cancer Institute Best Practices for Biospecimen Resources. 2011; 42 <http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf>.
62. Eiseman et al., *supra* note 56.
63. See generally International Society for Biological and Environmental Repositories, 2008 *Best Practice for Repositories: Collection, Storage, Retrieval, and Distribution of Biological Materials for Research*. Cell Preservation Technology. 2008; 6:241. available at <http://www.isber.org/bp/bestpractices2008.pdf>.

64. Beskow, Laura M., et al. Institutional Review Boards' Use and Understanding of Certificates of Confidentiality. *Public Library of Science One*. 2012; 7(9):e44050. at p. 5. [PubMed: 22962599]
65. Leslie E. Wolf et al., *supra* note 36.
66. Wolf, Leslie E., et al. Certificates of Confidentiality: Legal counsels' experiences with and perspectives on legal demands for research data. *Journal of Empirical Research on Human Research Ethics*. 2012; 7(4):1–9. [PubMed: 23086043]
67. *See generally* ANPRM, *supra* note 1.
68. ANPRM, *supra* note 1, at 44515.
69. The ANPRM defines “pre-existing data” as “data that were previously collected for purposes other than the currently proposed research study.” ANPRM, *supra* note 1, at 44519.
70. ANPRM, *supra* note 1, at 44519 citing Menikoff, Jerry; Richards, Edward P. *What the Doctor Didn't Say: The Hidden Truth about Medical Research*. 2006 New York, NY Oxford University Press: 113–123.
71. ANPRM, *supra* note 1, at 44519. (emphasis added).
72. ANPRM, *supra* note 1, at 44519.
73. ANPRM, *supra* note 1, at 44519.
74. ANPRM, *supra* note 1, at 44519.
75. ANPRM, *supra* note 1, at 44519.
76. ANPRM, *supra* note 1, at 44519–20.
77. ANPRM, *supra* note 1, at 44519, at 44522.
78. ANPRM, *supra* note 1, at 44523.
79. ANPRM, *supra* note 1, at 44524.
80. ANPRM, *supra* note 1, at 44524.
81. ANPRM, *supra* note 1, at 44524. For more information concerning the reidentifiability of DNA, see Lowrance, William W.; Collins, Francis S. Identifiability in Genomics Research. *Science*. 2007; 317:600–602. [PubMed: 17673640]
82. ANPRM, *supra* note 1, at 44526.
83. ANPRM, *supra* note 1, at 44526. See 45 C.F.R. pt. 160 and Subpart A and C of pt. 164 for further detail about the HIPAA Security Rule.
84. ANPRM, *supra* note 1, at 44526.
85. ANPRM, *supra* note 1, at 44526.
86. ANPRM, *supra* note 1, at 44524. Further, some individuals may object to at least some uses of their biological materials without consent. These objections can be seen in the several lawsuits that have been brought by patients objecting to use of their biological materials for research purposes. *See Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990); *Greenberg v. Miami Children's Hosp. Research Inst., Inc.*, 264 F. Supp. 2d 1064 (S.D. Fla. 2003); *Wash. Univ. v. Catalona*, 490 F.3d 667 (8th Cir. 2007); *Havasupai Tribe v. Ariz. Bd. of Regents*, 204 P.3d 1063 (Ariz. Ct. App. 2008). For further discussion and analysis of these cases, see Wolf, *supra* note 3, at 103.
87. The ANPRM's proposal in this regard has been criticized, representing the larger debate on biobanking. Some have argued that such a broad consent for research (especially in the clinical context) is not *informed* consent; rather, they argue, consent must be to specific research projects to be effective. Others have argued that the proposal goes too far by requiring consent to all research, even when specimens are deidentified. *See Nietfeld et al.*, *supra* note 7 for a discussion of these debates. For purposes of this paper, we set those arguments aside and focus on the ANPRM's proposals as they relate to Certificates.
88. Goddard et al., *supra* note 9, at 120.
89. GWAS, *supra* note 12; National Cancer Institute, Department of Health and Human Services, Office of Biorepositories and Biospecimen Research. National Cancer Institute Best Practices for Biospecimen Resources. 2011; 42 <http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf>.
90. NCI, *supra* note 61.

91. NCI, *supra* note 61.
92. GWAS, *supra* note 12, at 6. Law enforcement officers frequently used DNA data as evidence in their investigative work. Stored in the Federal Combined DNA Index System (CODIS), samples may be connected with samples from state databases as well. Additionally, the federal government now allows for the collection of DNA evidence from suspects upon arrest and, as of September 2011, twenty-five states have followed suit. *See, e.g.*, 42 U.S.C. § 14135a(a)(1)(A) (2011) (“The Attorney General may, as prescribed by the Attorney General in regulation, collect DNA samples from individuals who are arrested, facing charges, or convicted or from non- United States persons who are detained under the authority of the United States.”); KAN. STAT. ANN. § 21–2511(e)(2) (2010) (“[A]ny adult arrested or charged or juvenile placed in custody for or charged with the commission or attempted commission of any felony ... shall be required to submit such specimen or sample at the same time such person is fingerprinted pursuant to the booking procedure.”); N.C. GEN. STAT. § 15A-266.3A(b) (2011) (“The arresting law enforcement officer shall obtain, or cause to be obtained, a DNA sample from an arrested person at the time of arrest, or when fingerprinted. However, if the person is arrested without a warrant, then the DNA sample shall not be taken until a probable cause determination has been made pursuant to G.S. 15A-511(c)(1)”).
93. GWAS, *supra* note 12, at 6. Further, some have noted that law enforcement officers will seek to subpoena the tissues and genetic information of family members of a criminal suspect in order to find a match and support probable cause. Brown, Teneille; Lowenberg, Kelly. Biobanks, Privacy, and the Subpoena Power, *Stanford Journal of Law. Stanford Journal of Law, Science & Policy*. 2010; 1:89–101. 89. available at <http://www.sjls.org/?q=node/57>.
94. GWAS, *supra* note 12, at 6.
95. P.L. 110–233, 122 Stat. 881 (2008).
96. McGuire, Amy L.; Majumder, Mary Anderlik. Two cheers for GINA? *Genome Medicine*. 2009; 1(1):6.1–6.3. OHRP re GINA. [PubMed: 19348693]
97. McGuire & Majumder. *supra* note 96, at 6.2.
98. GWAS, *supra* note 12, at 6. “Further, the NIH takes the position that technologies available within the public domain today, and technological advances expected over the next few years, make the identification of specific individuals from raw genotype-phenotype data feasible and increasingly straightforward.” GWAS, *supra* note 12, at 6.
99. McGuire, Amy L.; Gibbs, Richard A. No Longer De-Identified. *Science*. 2006; 312:370–371. 370. [PubMed: 16627725]
100. Homer, Nils. Resolving Individuals Contributing Trace Amounts of DNA to Highly Complex Mixtures Using High-Density SNP Genotyping Microarrays. *Public Library of Science Genetics*. 2008; 4:e1000167. at 7, available at <http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1000167>. [PubMed: 18769715]
101. McGuire & Gibbs, *supra* note 88, at 370.
102. Wolf et al. *supra* note 66; Wolf et al., *supra* note 36.
103. Recent lawsuits over research use of newborn blood spots without consent resulted in the destruction of millions of specimens in Texas, which illustrates how dependent research is on public trust. Olson, Steven; Berger, Adam C. Rapporteurs. Roundtable on Translating Genomic-Based Research for Health Board on Health Sciences Policy. Institute of Medicine. Challenges and Opportunities in Using Residual Newborn Screening Samples for Translational Research. 2010 Washington, D.C. The National Academies Press:20–24. 26–29.at 2
104. ANPRM, *supra* note 1, at 44525.
105. Beskow et al., *supra* note 64; Wolf et al., *supra* note 66.
106. Wolf et al., *supra* note 66; Wolf et al., *supra* note 36. According to the interviews we conducted, Certificates may be effective as a deterrent and, when data are produced, they are deidentified, sometimes with other protections, such as promises not to try to reidentify. *Id.*
107. ANPRM, *supra* note 1, at 44519.
108. Brown, *supra* note 85, at 87; Eisemen et al., *supra* note 56, at 134 (“Ideally, the consent process should occur separately from surgical consent.”).
109. *See supra* Section Advanced Notice of Proposed Rule Making: Changes to Consent of Biospecimen Collection.

110. See Catania, Joseph; Wolf, Leslie; Wertlieb, Stacey; Henne, Jeff; Lo, Bernard. Research Participants' Perceptions of the Certificate of Confidentiality's Assurances and Limitations. *Journal of Empirical Research on Human Research Ethics*. 2007; 2:53–59. [PubMed: 19385807]
111. Wolf, Leslie E.; Zandecki, Jolanta. Sleeping Better at Night: Investigators' Experiences with Certificates of Confidentiality. *IRB: Ethics & Human Research*. 2006; 36:1–7.
112. Wolf, Leslie E.; Zandecki, Jolanta; Lo, Bernard. The Certificates of Confidentiality Application: A View from the NIH Institutes. *IRB: Ethics & Human Research*. 2004; 26:14–18. 14. (2004). [PubMed: 15281213] (describing a situation in which failure to have an IRB-approved consent form resulted in rejection of a Certificate of Confidentiality grant).
113. See *supra* Section Use of Certificates of Confidentiality for Biospecimen Research; ANPRM, *supra* note 1, at 44524. See also Paul Ohm, Broken Promises of Privacy: Responding to the Surprising Failure of Anonymization, *University of California Los Angeles Law Review* 57 (2010): 1701–1777, 1704 (2010) (arguing that emerging technologies have rendered research data “either useful or perfectly anonymous, but never both”).
114. 45 C.F.R. § 164.512(a) (2012); NIH, *supra* note 41, FAQ G.1.
115. Beskow et al., *supra* note 64; Wolf et al., *supra* note 66.
116. Wolf et al., *supra* note 112.
117. ANPRM, *supra* note 1, at 44524.
118. ANPRM, *supra* note 1, at 44522.
119. See Catania, *supra* note 110.
120. Paasche-Orlow, Michael K. Readability Standards for Informed Consent Forms as Compared with Actual Readability. @@@Using the Flesch-Kincaid readability scale, the investigators found that IRB's generally fail to meet the IRB's own standards for readability. *New Eng. J. Med.* 2003; 348:721–726. available at <http://www.nejm.org/doi/full/10.1056/NEJMs021212#t=article>.
121. Paasche-Orlow, et al., *supra* note 119.
122. We used the Flesch-Kincaid Readability scale incorporated into Microsoft Word™ to calculate the readability of the Certificate language. This is the same scale used by Paasch-Orlow, et al., *supra* note 119.
123. Paasche-Orlow et al., *supra*, note 119, citing National Work Group on Literacy and Health. Communicating with Patients who have Limited Literacy Skills. *Journal of Family Practice*. 1998; 46:168–176. (1998). [PubMed: 9487325] Later literacy assessments have reported similar levels. National Center for Education Statistics. A First Look at the Literacy of America's Adults in the 21st Century. 2005 available at <http://nces.ed.gov/pubsearch/pubsinfo.asp?pubid=2006470>.
124. NIH, *supra* note 41, FAQ C.3.
125. Beskow et al., *supra* note 64.
126. Beskow, et al., *supra* note 64.
127. 42 U.S.C. §299c-3 (protecting data collected or supported by the Agency for Healthcare Research and Quality) and 42 U.S.C.A. § 242m (protecting data collected by or supported by the Centers for Disease Control and Protection).