2013 HIPAA Changes Provide Opportunities and Challenges for Researchers: Perspectives from a Cancer Center

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Abstract

In 2013, the U.S. Department of Health and Human Services modified the Health Insurance Portability and Accountability Act Privacy Rule to “strengthen privacy and security protections” while “improving workability and effectiveness to increase flexibility for and decrease burden on regulated entities.” In this article, we attempt to translate these generalized goals into the real-world implications of these changes. Under the new rules, researchers can obtain participants’ permission to use their protected health information for more research activities with a single, upfront authorization (thereby reducing paperwork for participants, researchers, and institutional review boards) while providing potential participants with more information upon which to base their decisions about participation. The combined authorizations can be used in clinical trials and their optional substudies and in stand-alone biospecimen-banking research that includes authorization to permit future research use. We also suggest best practices for taking advantage of the flexibility offered by the new rules while maintaining strong privacy protections for human subjects.

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Learning Objectives

Upon completion of this activity, the participant should have a better understanding of recent changes to the Health Insurance Portability and Accountability Act regulations and how researchers could potentially benefit from their application. The participant should also have a better understanding of institutional review board processes related to protected health information and certain best practices for privacy protection involving biospecimens maintained in biodata repositories and data from tumor registries utilized in research.

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Introduction

In human subjects–based research, the retrieval of clinical data from a number of sources and the seamless linkage of such data to biologic specimens are critically important to translating new concepts in biology and tumor genetics into improved patient care and outcomes. However, those actions must be balanced against the requirement to protect patient privacy, a challenging objective in an era marked by increased risks linked to movement of large amounts of data and the accelerated development of genomic technology. Some recent changes to the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (1) could potentially and safely enable even large data-based human
subjects research projects, provided that efficient processes have been established for securing and releasing protected health information (PHI). Institutional oversight groups, such as institutional review boards (IRB), should continue to scrutinize current and future biodata-driven research for the potential to add risks to privacy and to ensure that explicit information is provided to potential subjects upfront for future research.

In this article, we discuss the key regulatory changes and how they may affect both clinical and biobank/data-driven research. We also discuss briefly the role of IRB oversight, and how increased flexibility in the revised HIPAA rules allows for more creative design of data- and tissue-banking protocols, enabling the resources of large institutional databases to be combined for future research activities while privacy protections are addressed at research data and tissue access points.

Key Regulatory Changes as They Apply to Human Subjects-Based Research

Several HIPAA Privacy Rule changes, enacted in 2013, are of particular relevance to the access and use of data for human subjects research. These changes include (i) permission to obtain a single authorization to use PHI in both "conditioned" research activities (such as clinical trials, in which individuals cannot receive a particular treatment unless they agree to the use of their PHI) and "unconditioned" research activities (such as optional tissue and data banking, in which individuals can receive a particular treatment even if they do not agree to the use of their PHI; ref. 2); (ii) permission to simultaneously obtain authorization to use PHI in both current research (including stand-alone biobanking protocols) and future research, provided the future use of PHI is described with enough specificity that a reasonable person would expect that it would be used for that purpose (2); and (iii) clarification that, for the purposes of HIPAA, genetic information is "health" information, though not, on its own, identifiable (3). The Privacy Rule was amended to be consistent with the Genetic Information Nondiscrimination Act and to prohibit health insurers from using genetic information for underwriting purposes (4). However, neither prohibits long-term care insurers, life insurers, and disability insurers from using genetic information, potentially to a person's detriment; thus, although the Genetic Information Nondiscrimination Act and the Privacy Rule provide some protection for genetic information, these protections are limited (5).

How the changes have streamlined informed consent and authorization processes

Before 2013, separate HIPAA authorizations were required for a study with both a clinical trial component and a tissue- or data-banking component, even if both activities were part of a single protocol and described in one informed consent document. In addition, researchers who needed to use banked tissue and data in such a study would have to either seek a new HIPAA authorization from the participant or request a waiver from the IRB. For practical reasons, waiver requests were undoubtedly the more popular option; as a result, most study participants had little or no idea of how their data were eventually used. Furthermore, the waivers by themselves did little to protect participants' privacy.

In theory, the new HIPAA rules allow researchers to obtain, in a single authorization document, (i) permission to use a participant's data for a clinical trial; (ii) permission to bank the participant's tissue/data for future research, provided that the document clearly delineates the clinical trial and banking portions and provides an opt-in mechanism for the banking component; and (iii) permission to use the participant's data for future research, provided that the document includes a description of the research that has a degree of specificity that is acceptable to the IRB and gives the participant a reasonable idea about the nature of the research. Thus, the 2013 amendments align the HIPAA rules governing authorizations more closely with the rules governing informed consent in the current version of the "Common Rule" and with FDA regulations. This is helpful given the fact that these items are allowed to be combined in the research context (2). In all other contexts, HIPAA authorizations are required to be stand-alone documents.

Relevance of these changes to clinical studies

In clinical trials of experimental drugs and devices, unimpaired access to data is necessary both for the safety monitoring and auditing of subjects (2) and in the interests of research objectivity. Sponsors and external researchers may request and receive permission to access PHI for other activities. Any specific privacy protections for potential participants in clinical trials should be addressed in contracts or agreements between the covered entities and sponsors or between researchers at collaborating institutions. Informed consent and authorization documents should also make it clear to participants that future sponsors and collaborators might have access to their tissue and some of their identifiable data.

How is an IRB’s role affected by HIPAA modifications in biodata-driven research?

In its review of human subjects–based research (6), an IRB is obligated to ensure that risks are minimized and that the informed consent process adequately addresses risks (7–9). Whereas an IRB may review prospective research of existing biobanked tissues and data in the context of whether its risks equal or exceed "minimal risk" (6, 10), under HIPAA, "minimal risk" is used only in the context of privacy protection. The IRB is required to review and approve a combined informed consent and authorization document that supports the creation of a biobank. The IRB should be assured that sufficient information is provided to prospective participants, enabling them to decide whether they wish to opt-in for future research with the specimens and data (discussed in more detail below). Examples of the types of IRB processes or actions that could involve biobank-/data-driven future research studies are shown in Table 1 (11–18).

On September 8, 2015, the Department of Health and Human Services (HHS) published a notice of proposed rule-making (NPRM) with "revisions to modernize, strengthen, and make more effective the Federal Policy for the Protection of human Subjects" of the Common Rule of 1991 (19). Its purpose is to facilitate research and reduce "burden, delay, and ambiguity for investigators." Since the changes have not been finalized, only certain of the proposed changes are briefly mentioned here: The NPRM includes proposals to bring research use of de-identified biospecimens under IRB oversight, to exclude certain research involving only identifiable data from IRB oversight, and to promote use of an HHS-created template for obtaining consent to collect and use biospecimens and associated data. In short, the NPRM proposes to strengthen
protections for biospecimens, relax oversight of research involving only identifiable data, and give more power to individuals about whether their tissue can be used for research in the future (whether de-identified or not). Generally speaking, the proposed rule is consistent with the 2013 HIPAA rule changes discussed in this article (in that it indirectly encourages use of an honest broker system and encourages use of a banking consent template that could include an individual’s HIPAA authorization for future research use of their PHI), but it appears to underemphasize the HIPAA Privacy Rule’s heavy reliance on IRBs to oversee use of identifiable data in research.

In terms of IRB oversight as summarized in Table 1, the proposed changes may also move certain activities in the "exempt" or "expedited" review categories of research to a lower risk or unregulated activity.

### Protecting Patients’ Privacy in Banking Tissue and Data for Future Research

In the remainder of this article, we explore best practices for taking advantage of these new rules in the tissue- and data-banking context while maintaining strong privacy protections in...
an increasingly genetic-centric research environment. Under the new HIPAA rules, a biorepository protocol and matching informed consent and authorization document may state the intention to collect and store specimens and annotated data for future research, as well as to use that tissue and data for future research. Clearly, it would be impossible to describe all future uses with great specificity at the time of collection, but if sufficient information is provided to prospective research participants concerning the general purpose of tissue collections, any risk or benefits (if appropriate), and how risks are being mitigated, the initial consent and authorization may serve as permission to use the participant's data and tissue for both the present (banking) and future research purposes.

"Sensitivity" of future research and controversial or special issues that may arise

Certain types of future research pose more privacy risks than others and merit heightened IRB scrutiny to ensure that participants are adequately informed of those risks. In the tissue-banking context, future research activities may generate increasingly sensitive genetic information, such as that which can be linked to an individual, family members, or a community. In addition, whole-genome or -exome sequencing may enhance the risk of identifying unexpected deleterious genes outside of a protocol's purpose or goals. Given the current limited legal protections for genetic information, the informed consent and authorization document should highlight the potential for the generation of genetic information, explain how that information will be used and protected, and describe the potential risks associated with participating in a study that generates that type of information. In addition, many states require explicit consent to disclose such information, even in situations in which HIPAA would otherwise require consent. Therefore, obtaining a participant's explicit consent for the future use and disclosure of his or her genetic information for research (4, 20, and 21) is preferable to relying on an IRB waiver to use that information at some undefined point in the future.

Using banked tissues and data for future research raises some controversial questions about the bioethics and practicality of sharing information with participants. For example, should potential study participants be asked whether they would want to be informed of any abnormality discovered, or only those that are actionable and validated in a Clinical Laboratory Improvement Amendments–accredited laboratory? It may be unrealistic to provide long-term informational updates to tissue donors because certain mutations can change in significance over time and resources would have to be developed for following a mobile population. A possible answer to the first question is to focus on cancer-related mutations that could be of use to patients in future treatment or reproductive decisions or decisions related to clinical trial participation. If potentially deleterious genes are discovered and validated, subjects might also be informed whether specific counseling is available. Guidance is available on when to report genetic results (22).

Special consenting considerations may be required for potential research participants who are minors because they lack full decision-making capacity, and some authorities believe that minors should not be tested for mutations that are not actionable until adulthood.

If the future-proposed research is of a sensitive nature (e.g., psychological studies, studies involving a specific vulnerable population), a convened IRB decision would likely require a reauthorization for accessing and using the data or tissues. In such instances, regulations that apply to vulnerable individuals remain unchanged. Pertinent to biobank protocols, individuals who were minors at the time of initial consent should if possible be reconsented once they are 18 years old. Potential participants must be informed that they will have no proprietary interest in any discoveries made with their donated tissues and that such discoveries might be patented or licensed by the institution or others. Other protections include Data Use Agreements and a Certificate of Confidentiality from the federal government intended to protect individual participants from having their PHI used against them in certain legal actions.

Challenges in sample de-identification and subject identification from genomics

De-identified data or limited datasets should be used whenever feasible, as doing so protects individuals in the event that their data are lost or stolen. Limited datasets—data that lack all identifying information (save dates, locations by city, state, and zip code, and unique identifying numbers or codes)—allow limited amounts of PHI to be disclosed to researchers without the need for participant authorization or an IRB waiver (23).

Many investigators promise that tissue specimens will be de-identified prior to use, but tissue without identifiable data (information from the patient's medical record, for example) is often of quite limited value. One way to overcome this obstacle is to use an "honest broker" system (20), which maintains studies at "minimal risk" by enabling institutions to keep a centralized link between tissue specimens and identifiable data and implement centralized data governance, quality, and security controls, while minimizing the amount of PHI possessed (and potentially compromised) by researchers. However, conducting certain research without access to PHI—for example, complex multifactorial outcomes analysis of prior treatments or of tumors that express certain biomarkers or genetic mutations—may be impracticable.

The de-identification of samples can be complicated especially when multiple investigators wish to utilize tissue from the same patient. With simple coding practices, an investigator may unintentionally identify the patient, risking regulatory noncompliance. One solution to this problem would be for the tissue bank to include a one-way hash key that links the protocol to the de-identified patient. Thus, different protocols would receive different "context-associated" de-identified patient identifiers. The tissue bank, which would have access to the protocol's associated keys, could re-identify the patient, whereas researchers using the patient's tissue, who would not have access to the keys, would be unable to identify the patient. If an IRB were to later approve tissue sharing across certain protocols, the tissue bank would be able to re-identify the patients who donated the tissues.

Another common practice for attempting to de-identify patient samples is to number the samples sequentially. Although the NIH accepts the sequential numbering of samples as random, the practice still carries some risk of patient identification because of numerical proximity. A potential workaround for this issue is to either randomly assign numbers to the samples and/or use a new context-associated sample identifier (i.e., labeling system). However, replacing labels can
present a technical challenge, especially with frozen samples. Radiofrequency identifiers, which can be recoded, thereby facilitating the de-identification process, may eventually become the preferred labeling system.

In an era in which whole-genome sequencing is becoming increasingly common, the question of whether patients and/or their samples can be re-identified from unique tumor characteristics or from genomic data begins to be asked. For example, patients with rare tumors might be more easily re-identified, depending on the frequency of the tumor and whether the data have been aggregated.

In regard to genomics and subject identification, Gymrek and colleagues (24) were the first to investigate the possibility of using genomic data to identify patients. They compared short tandem repeats (STR) of the Y-chromosome (Y-STR) from genomic data with the same Y-STRs associated with surnames in genealogical databases, accounting for expected changes in STRs over generations. Their findings suggest that genomic data can be de-identified by removing the STRs or replacing them with randomized values. The researchers also demonstrated that surname-associated SNPs on the Y-chromosome (Y-SNP) could be used to impute the Y-STR genealogical haplotype; however, a 5% success rate using this approach requires a reference panel of 50,000 male genomes. This suggests that identifying patients from genomic data is a relatively small risk at present, but as community efforts to link Y-SNPs and surnames grow, the utility of masking Y-STRs to de-identify genomes will decrease, and the issue of de-identifying genomic material may have to be re-examined.

Currently, the Privacy Rule does not plainly label genetic information as “identifiable,” absent any of the traditional HIPAA identifiers (e.g., names, medical record numbers, dates, addresses). In light of the potential for using genetic information to re-identify patients, this guidance may be ripe for reconsideration by HHS. In the meantime, institutions, IRBs, and researchers must determine whether for specific studies de-identified genetic information can be re-identified by people with the right knowledge and tools and, if so, take steps to protect that information in a manner consistent with their protection of other PHI. In addition, informed consent and authorization documents must clearly explain that tissue collected under banking protocols may be subjected to genomic sequencing and identify the potential risks associated with the future use or disclosure of that tissue and resulting data.

The recent changes in HIPAA also provide opportunities for restructuring all institutional tissue repository protocols so that consent and authorization to use or reuse tissues also include future data use. Researchers at an institution can now obtain permission to collect tissues and access and use data under a single consent and authorization document, regardless of whether the tissues and data are specifically associated with a particular clinical therapy trial or collected for future use in a retrospective study of survival outcomes associated with one or more biologic markers with linkage to multiple important demographic characteristics. By providing appropriate lay descriptions of future uses (e.g., “genomic profiling,” “manufacture of cell lines,” “epidemiology,” and “immune studies”), researchers can enable prospective subjects to make informed decisions about whether their tissues and data can be used for future studies.

Maximizing Research Potential of a Tumor Registry While Maintaining Privacy Protections: The MD Anderson Strategy

Tissue-based research is most valuable when annotated by a rich, structured clinical data resource not directly visualized in a medical record. MD Anderson’s Tumor Registry, which dates back to 1944 and provides mandatory reports to the Texas State Tumor Registry, has approximately 1,066,000 patients in its database (25). The database codes all malignancies over a patient’s lifetime, including previous cancers treated elsewhere and benign neoplasms, as well as comorbidities that could affect the patient’s outcome. The database also contains basic demographics such as sex, birth date, and race as well as the following clinical variables: cancer site, tumor histology, cancer stage (both American Joint Committee on Cancer stage and Surveillance, Epidemiology, and End Results Program stage), cancer treatment received within the first 4 months of diagnosis, and subsequent therapy. The MD Anderson Tumor Registry has follow-up information, including vital status and date of last contact or death, for more than 90% of its patients. The registry functions under standard operating procedures using national standards (26, 27) and performs quality controls to ensure data recovery and accuracy. An institutional data warehouse and a front-end search engine for aggregate counts are available to appropriately trained institutional investigators.

Tumor Registry data can be merged with annotated data from the Institutional Tissue Bank. Users can see in real-time each patient’s vital status and identifying information. Tumor Registry data can also be supplemented with data from other institutional databases. Information that has been combined using clinical attributes to filter or annotate tissue from the Institutional Tissue Bank is available via a portal. Users who have delegated authority under a specific study protocol can view detailed tissue and annotation data for each sample from patients on that protocol. Users who are not associated with a specific protocol but are members of the institution can perform a search filtered by specific clinical characteristics that returns de-identified results limited to the bank or protocol that has custody of the tissues meeting the search criteria, the numbers of patients and samples in custody of that bank or protocol, and contact information for the bank or protocol. This function is frequently used to determine sample availability. Currently, it can also be used to identify archived samples that can be requested given a use protocol with a waiver of informed consent based on a patient’s prior front-door consent or protocol-specific consent. Going forward, this latter application will benefit from the recent HIPAA changes undoing the requirement that additional authorization must be obtained for the future use of specimens as long as permission for the future use was obtained upfront in the original consent and authorization document. Researchers wishing to view additional detailed information about individual samples must obtain authorization and permission from both the clinical database and the biospecimen repository, a practice similar to that employed by the pan-European Biobanking and Bimolecular Resources Research Infrastructure (28, 29). Thus, users can combine data resources for both clinical- and tissue-based data. In addition, this model lays the groundwork for an electronic “honest broker” system that uses a medical record number or
other PHI not accessible by the investigator to pull information from other databases. Honest broker systems are not standardized across institutions. However, the development of efficient systems has the potential to protect biosamples in adequately designed repositories, and protect privacy at the interface between the biorepository and the researcher (20). It bears emphasizing that the application of privacy protection regulations for biodata repositories should be accompanied by complementary privacy and security protection procedures in the biorepositories.

Conclusions

The 2013 HIPAA modifications are a practical step toward harmonizing the regulations of the various HHS subagencies. The timing of the modifications coincides with unprecedented progress in research on diseases such as cancer and an increasing need to interrogate tissue sample biology with clinical data. Adapting to these changes requires more and better privacy-related information for potential research participants, sophisticated tissue- and data-banking resources, and a supportive regulatory infrastructure. At the same time, technological advances in genetics, and an increasing ability to identify people from their DNA, will place individual privacy at risk. This article shows how the flexibility afforded by the HIPAA modifications and their harmonization with other regulations potentially benefit the data paths supporting human subjects-based research while strengthening privacy protections overall.

Authors’ Contributions

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