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Learning Health Systems

EXPERIENCE REPORT

Transparency and choice in learning healthcare systems

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Abstract

Learning healthcare systems rely on potentially sensitive data and biospecimens from patients who typically have no knowledge of secondary uses of these resources for research. While this failure to inform patients of these practices is consistent with human subject regulations for research, these practices risk controversy and a loss of trust in the integrity of healthcare institutions. This article reviews recent controversies in this domain and argues for new institutional practices that entail patient education about secondary uses of data and biospecimens and the opportunity for patient choice in the form of an opt-out system. This approach would enhance transparency and reduce the risk of a loss of public trust in the research enterprise.

KEYWORDS

biobanking, ethics, informed consent, opt-out, learning healthcare system

The premise of a learning healthcare system is that data collected in course of the routine clinical care of many individuals can be systematically analyzed to enhance the quality of patient care. Freidman et al describe the concept:

> *[T]he underlying concept is straightforward: harness the power of data and analytics to learn from every patient, and feed the knowledge of "what works best" back to clinicians, public health professionals, patients, and other stakeholders to create cycles of continuous improvement.*[1]

The advent of electronic health records makes this effort feasible, along with the existence of health systems that care for hundreds of thousands or millions of patients over time. While the prospects for substantial improvements in the quality of care are exciting, there are a host of challenges in obtaining meaning conclusions from these datasets. From an ethical perspective, a central issue is how to maintain the trust of patients and their families when sensitive data are being accessed and used for secondary purposes, that is, purposes beyond the welfare of the source individuals. While trust is not essential to acquiring data or to data analytics, trust is essential to any system that seeks to endure in this sensitive healthcare space. I will argue that 2 keys to deserving and maintaining trust are transparency about policies and practices, and an element of patient choice for secondary uses of data and biospecimens (DAB).

In recent years, a substantial literature has grown on ethical and regulatory issues in the secondary uses of biospecimens and data for research purposes.[2,3] For this chapter, I will not make a distinction between DAB for the simple reason that biospecimens are only useful if they are associated with data about the source individual (gender, diagnosis, treatment history, family history, racial group, etc) and biospecimens are only useful to create new data through the analysis of the sample. Further, I assume that the learning healthcare systems will seek to use biospecimens acquired in clinical care in basically the same fashion that data are used. I understand that some individuals and cultural traditions may view biospecimens differently than data because specimens are pieces of the physical body, but this distinction will only serve to support my arguments regarding transparency and choice. Further, I will not make a large distinction here between research and quality assurance (QA)/quality improvement uses of DAB. Although there has been much discussion of biobanks in other national and international contexts, my focus will be on the US system.

A core element of a learning healthcare system is the use of stored DAB obtained in clinical care from large numbers of individuals over time. Accordingly, the research uses of DAB are typically removed in time and space from the acquisition of these resources from the source individual. This gap leaves 3 options regarding traditional informed consent from patients. Consent might be obtained at the time of a clinical encounter for future, unspecified use of DAB. Second, individuals

could be recontacted for consent for broadly described future uses or for each use. Third, informed consent could be waived in one manner or another. Without question, the preferred approach has been to waive consent for research with DAB acquired clinically. This is permissible under the federal regulations governing human subject research, 45CFR46, through either 1 of 2 mechanisms. If the DAB are deidentified to the investigator, then the research does not constitute human subject research, and neither institutional review board (IRB) review nor informed consent is required. Unless longitudinal data collection about the health of the source individuals is necessary, deidentified DAB are adequate for most research. Alternatively, an IRB may approve a waiver of consent if the 4 criteria under 45CFR46.116(d) are met. The 2 key criteria in this context are that the research must be minimal risk and obtaining informed consent must be deemed impracticable. Research with DAB obtained clinically typically meets these criteria. The track record for this type of research has been excellent with respect to any risk posed to source individuals and the separation in time and distance between investigator and source typically means that consent is impracticable. A number of scholars in this domain support the conduct of much of this research without informed consent.[4,5]

While the lack of informed consent for research on DAB is perfectly acceptable under the regulations and can be justified ethically, this approach leaves patients in the dark. Other than patients who work in the healthcare arena, a large majority of individuals have little or no idea that their data and residual biospecimens might be used in biomedical research.[6,7] In some institutions, this information might be included in agreements that patients routinely sign on admission to a hospital. At the University of Utah, our admission agreement simply notes that residual tissues may be discarded or used in a manner consistent with state and federal law. Such statements and documents fall well short of any reasonable notion of informed consent. Further, patients cannot "line-out" a phrase if they happen know that such language means that the institution can use their tissues for research or other nonclinical purposes. From the research institution's perspective, the failure to provide information to patients regarding this practice has distinct advantages. No one becomes upset or worried about potential breaches in privacy or confidentiality and investigators can work with a complete dataset, unbiased by refusals to consent that may not occur randomly within the patient population.

Three controversies in the last 20 years illustrate that this traditional approach is not all well and good. In 2000, the Havasupai Indian Tribe sued Arizona State University for secondary uses of biospecimens, arguably without the informed consent of participating tribal members.[8] The members of the tribe understood that the purpose of the research was to evaluate genetic underpinnings of diabetes, a serious health problem for the tribe. The consent form language was ambiguous and tribal members claimed that they were not aware of the potential for secondary uses of the specimens. The primary investigators and the institution subsequently shared the specimens with other investigators who conducted research on issues considered sensitive by the Havasupai, including mental health conditions and ancient migration patterns. Arizona State eventually settled the suit with the tribe but not before the controversy exacerbated distrust and chilled research participation by many native peoples. This case is familiar to those in the research ethics and regulation fields and has fostered a greater awareness of risks of group stigmatization even when individual level data or biospecimens are deidentified.

A second controversy arose in 2009 when several groups of parents independently sued the state health departments in Minnesota and Texas for the secondary use of residual newborn screening bloodspots without parental consent.[9] Newborn screening is conducted by all states in the United States for 30 or more conditions, most of which are genetic in origin. A characteristic feature of newborn screening is that it is conducted without parental permission. Screening uses dried bloodspots that are sent to state laboratories, or their partners, for analysis. In almost all cases, there will be residual blood leftover after clinical testing is complete. These residual bloodspots have been extremely useful for QA purposes and for biomedical research. A particularly useful aspect of this resource is that the bloodspots represent virtually every newborn in a state's population. While not all states save the leftover bloodspots, many do and some states will save the specimens indefinitely. Traditionally, information about this practice was offered in a sentence or 2 in a brochure that is distributed to new parents after the birth of their baby. However, these brochures are ineffective tools, particularly at this hectic time for new parents. Most parents have no idea about the retention and potential research use of residual bloodspots.[10]

When parent groups in Minnesota and Texas learned of these practices, they brought suit, although the legal claims in the 2 actions differed. The legal history of these cases is complex, but, suffice it to say, millions of stored bloodspots in both states were destroyed in response and new policies were put in place to obtain the consent of parents to retain and use residual bloodspots.

These suits alarmed health departments across the county but the issue did not remain at the level of state governments. In 2014, the Federal Government passed the Newborn Screening Reauthorization Act of 2014 that included a new section prohibiting the use of residual bloodspots without parental consent.[11] Further, the law prohibited the waiver of consent even when the waiver criteria under 45CFR46 were met. This law halted virtually all secondary research uses of these valuable specimens as some states scramble to implement informed consent processes for residual bloodspots.

The third controversy was over a case that is over 60 years old, brought to life with the publication by Rebecca Skloot of her popular book, *The Immortal Life of Henrietta Lacks*.[12] The book presents the story of the woman who was the source of the first cell line successfully cultured in the laboratory, HeLa cells, that proved enormously useful for a broad range of studies. Readers are left with a clear sense that Mrs. Lacks and her family were ill-treated by investigators at Johns Hopkins University both because they did not obtain informed consent for research and because the family never received compensation for what became a commercially valuable line of cultured cells. The author clearly presents the fact that ethical standards in the retention and research use of clinical samples and data have not changed much since Henrietta Lack's day. That is, consent is still not required for secondary research uses of these resources, nor is there any interest in developing compensation schemes for those who provide samples or data that prove valuable for commercial products.

These cases and other research illustrate that members of the general public have several types of concerns over research uses of biospecimens without the individual's permission. In our own research, we find that the lay public has only a very limited understanding of what biomedical research entails, along with its benefits and risks.[6]

People can articulate general benefits, like improvements in health care, but often struggle with specifying risks or fears. A common concern from parents about research uses of newborn screening bloodspots was the prospect of cloning a baby. The protection of individual or family privacy is a major concern for many, particularly with research involving DNA analysis.[13] There is a prevalent belief that our DNA contains a host of personal information that is sensitive, creating risks of stigma or discrimination if not adequately protected. While the fears associated with genetic research may be out of proportion to the true risk involved, these concerns are clearly legitimate. A more general, principle-based objection to research without permission arises from the sense for many that people "own" their biospecimens and respect demands that investigators seek permission for their use.[13] Other types of concerns may arise from cultural or religious traditions and historical experiences. As noted, the Havasupi case arose from objections to any research being conducted beyond the primary purpose of the DAB collection and from objections to the sensitive nature for their community of those particular projects.[8] This case highlights the importance of understanding the beliefs, traditions, and history of communities for investigators and IRBs when conducting research in a cross-cultural environment, and particularly with communities that are underserved or vulnerable.

In response to these controversies and debates, changes in the federal rules governing human subjects research were proposed in 2015 by the Department of Health and Human Services. The Notice of Proposed Rulemaking (NPRM) contained numerous proposed changes in the regulations to both enhance safety of research participants but also to reduce regulatory burdens of the oversight system. For the purposes of this chapter, the proposed changes in the management of biospecimens will be highlighted. The NPRM made a distinction between tissues and data, and it would have required the informed consent of the tissue source for any secondary research use of tissues acquired in clinical care. The consent for such use could be open-ended, meaning patients could be asked permission for future, unspecified uses. However, the required consent elements were rather lengthy and detailed. Further, once consent for secondary use was obtained, investigators need not obtain IRB review or approval for research, as long as data security measures were in place.

The rationale for requiring broad consent for biospecimen research was a perceived obligation to inform patients of this practice and to honor their autonomous choice. However, the NPRM in this respect was strongly opposed by the biomedical community. The concerns expressed from the research community were several fold. First, the consent document is relatively complex, meaning that a true informed consent would require a significant investment of time on the part of staff to talk through and explain the content. This would not be feasible as part of most routine clinical care where patients and staff are otherwise occupied with whatever health concerns brought the patient to the hospital or clinic. Admitting staff and clinicians are often not familiar with research practices using biospecimens so they would not be in a good position to obtain consent and respond to questions or concerns. Therefore, more than likely, consent forms would be presented as routine forms to sign and would be signed with cursory or no review, thus undermining the purpose of the consent process. Second, institutions would need to track the choices of each of the tens or hundreds of thousands of patients who obtain care in these facilities, choices that may change between visits, and assure that those choices were honored when investigators sought access to samples. This would be an extraordinary logistical challenge, likely requiring large financial investments in software and personnel to develop and maintain. Third, the lack of oversight for any research, once consent had been obtained, means that cases like the Havasupai Tribal case could occur again. That is, controversial or sensitive research could be conducted without any oversight from the institutions where patients sought their care. In summary, the criticism was that broad consent would be ineffective, highly complex, and expensive to institute and would not prevent abuses of trust by those choosing to seek care in these institutions.

Both the NPRM and the Newborn Screening Reauthorization Act illustrate discomfort at the level of the federal government with contemporary standards of consent for research with DAB. Surveys of public attitudes also consistently demonstrate a desire for greater engagement with patients about these practices.[13] The final regulations that emerged from the NPRM process were published in January 2017 and will go into effect in January 2019. The new rules contain none of the complex and controversial changes proposed in the NPRM with respect to biospecimens. Research with deidentified biospecimens and data will remain nonhuman subject research and therefore will not require IRB oversight or consent. However, if biospecimens are acquired in research and banked for future uses, there are new requirements for informed consent. These include the following:

> 45CFR46.116(b)[9] (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
>
> (ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.
>
> 45CFR46.116[7] A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit; …
>
> [9]For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (ie, sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

The new regulations also provide a provision for broad consent for secondary uses of biospecimens and data if the investigators wish to keep identifiers with the DAB and they do not wish to seek a waiver of consent. The requirements for broad consent are detailed and will be paraphrased here. These requirements are found at 45CFR46.116(d) and are in addition to the standard requirements for informed consent:

> (2) A general description of the types of research that might be conducted with the DAB.

(3) A description of the DAB that might be used in research, whether sharing might occur, and the types of institutions with which sharing might occur.

(4) A description of the time period that DAB might be stored and might be used for research.

(5) Unless the subject will be provided details in specific research studies, a statement must be included that the subject will not be informed of details of the research, including its purpose and that they might have chosen not to consent to some of the specific research studies

(6) A statement that all research results may not be disclosed to the subject

The purposes of these changes are several fold. As noted, the utility and safety of research with deidentified DAB has been substantial, as was the backlash from the biomedical community when burdensome changes were proposed in the NPRM. To a large extent, this burden would have precluded use of clinically acquired DAB without consent. The new regulations do not require engagement of patients regarding secondary uses of DAB. However, when prospective participants in research are engaged in a consent process, the new regulations require a substantially more robust set of disclosures about secondary uses of DAB and what participants might expect in future contact, information about the research uses, and results. These new requirements in the research context will lead to longer forms and perhaps a longer consent process but they will enable investigators to use identifiable DAB for a broad range of future projects. Broad consent is likely to be the preferred approach for investigators and institutions that seek to link clinical records on an on-going basis to research resources like biobanks.

The gap or flaw in this new schema remains the lack of awareness and consent by patients for secondary research uses of their DAB acquired in clinical care. The lack of any basic transparency or choice has been central to several of the most high-profile public controversies. From the investigator's perspective, such uses without consent may seem to be ethically acceptable because of the high utility and low risks associated with this practice. Unfortunately, the general public is not aware of the practice and thus not aware of its utility for medical science. Further, many or most members of the general public are not aware of safeguards in place such as the federal regulations and oversight by IRBs. In our own work, we found that most individuals simply assumed that clinical records were private and that residual clinical biospecimens were discarded as waste.[6] Accordingly, their awareness of a common, large-scale enterprise to use clinically acquired DAB in research comes as something of a shock and can engender concern and distrust. They may think, "If this is all so innocent, how come no one told me about it?" Trust by the general public in the research enterprise can be lost even when investigators, sponsors, and institutions are playing by the rules.

The challenge in this context is to strike the right balance given, on the one hand, the value of secondary uses of DAB to science and health care, and, on the other hand, the sensitivity many members of the public have over these practices. For the reasons discussed, a required informed consent process for all patients for such secondary uses is highly likely to be ineffective in acquiring autonomous authorization, burdensome to institutions, and damaging to the research enterprise. This damage is not primarily due to a large proportion of people declining access to their DAB but to an inability of hospital staff to effectively obtain and record consent during busy clinical services.

An appropriate compromise for learning healthcare institutions is a policy of notice and opt-out. The basic concept is that patients at learning healthcare institutions would be routinely informed about institutional policies regarding secondary uses of DAB for research purposes. For those patients who objected to such uses, they could choose to opt-out, precluding use of their DAB for research purposes. The advantage of this approach is that it meets the expectations of many in the general public for 2 elements—they want to be told about what happens with their DAB and they want a choice over secondary uses.

The ethical justification for a notice and opt-out approach builds on the work of Miller and Wertheimer who developed a "fair transaction model for informed consent.[14] They argue that "The criteria for assessing the validity of consent transactions should be based on fair terms of cooperation for the respective parties that reflect the context of the activity for which consent is given." A fair process is one that is fair for both the subject of research and the investigator. Accordingly, high-risk research requires a high level of autonomous authorization by participants and low-risk trials require only limited level of authorization, or perhaps no authorization at all. In the context of learning healthcare systems, risks to patients are extremely low for secondary uses of DAB yet we know that when asked, they wish to provide some level of authorization for these practices. A policy of notice and opt-out arguably achieves fairness for both parties in that, for patients, they are offered information and choice and, for investigators and institutions, the effort would not unduly burden the clinical or research enterprises. We know from other contexts where notice and opt-out are offered, the large majority of individuals do not choose to opt-out, thus maintaining the integrity of the research resource for valuable studies.

There are a variety of considerations and challenges in making a notice and opt-out system ethically justifiable and functional. The notice would present information about the institutional practice regarding secondary uses of DAB and the safeguards in place to protect privacy and confidentiality. The disclosure could take many forms, but it must be sufficiently robust to count as a good-faith effort to inform people. If the notice is buried in another lengthy document, then it would be routinely overlooked by virtually everyone. This sort of disclosure might meet the legal interests of the institution in having offered notice, but it would not represent a good-faith effort at communication and transparency. So the notice needs to be in plain language, whether presented on paper or by audiovisual media, and offered in a place that welcomes the patient's attention. We also know that a large proportion of people are not very interested in these issues, particularly when they have other healthcare concerns that brought them to the hospital or clinic. But a small proportion of the population will be interested. To accommodate the variable levels of interest that different people will have, it would be ideal to offer the notice in a layered form. By this, I mean people would be able to dig deeper into the subject if they are interested. The basic notice could

be short and simple, but those who want more information would be able to acquire that readily. This sort of layered document can be effectively supported through digital media. One possibility would be to send the notice to patients via email when they make an appointment, and once a year or so thereafter. The disclosure could be in a format that enables people to follow links to a more detailed set of information or resources about the policies and practices of their learning healthcare institutions, if they so wish.

Similarly, the ability to opt-out should not be burdensome. For example, requiring people to call an administrative office at the institution during limited hours of the week would effectively preclude the ability of all but the most motivated person to effectuate their choice. However, given the value of DAB to learning healthcare institutions and the public's health, it may be appropriate to establish some minor barriers to record a decision to opt-out, such as a required review of the notice. A minor barrier will encourage people to give the issue some thought and have at least a minimal level of motivation to enact their choice.

The notice and opt-out approach is certainly consistent with the traditional and new federal regulations that actually require no disclosure or choice for secondary uses of DAB. As noted, the traditional approach is strongly supported by the biomedical community and is supported many ethicists and policy makers due to its value and demonstrated safety. We have found in our research with the general community that notice and opt-out is an acceptable institutional policy when people have a broader understanding of the issues and tradeoffs involved.[6] More direct evidence of the value of this approach comes from the experience at Vanderbilt University with the creation of their BioVU biobank.[15] The BioVU is a collection of biospecimens from residual blood obtained from patients at Vanderbilt that are linked to their electronic medical records. BioVU has a complex encryption system that permits the specimens to be deidentified to investigators while maintaining a longitudinal link with the electronic medical records so that specimen analysis can be informed by changes in clinical status of the patient. Until recently, BioVU used an opt-out model in which patients reinformed of the secondary uses of biospecimens and clinical records and they can opt-out of such uses. Vanderbilt did extensive community engagement prior to launching the BioVU and found that greater than 90% of those surveyed supported the opt-out approach.[16] During the period of time when BioVU was using the opt-out approach, those choosing to opt-out were about 15% of patients, a number that is sufficiently robust to indicate that many patients were aware of their options.[17] The BioVU changed to an opt-in model when the National Institutes of Health adopted a policy requiring consent for the posting of sequence data on a publically accessible database, dbGaP.[18] Therefore, Vanderbilt moved away from the opt-out model not because the system was not working well but because of external requirements by the National Institutes of Health.

Research and the experience of projects like BioVU indicate that the notice and opt-out approach is feasible and can promote a high level of participation while promoting transparency and giving patients meaningful choice. Of course, implementing a notice and opt-out in learning healthcare systems for secondary uses of data and tissues for research and QA/quality improvement would not be easy. Communication tools and systems for effective notice and choice need to be designed, tested, and implemented. Data documenting patient choice can be associated with the biospecimen or otherwise available in a dataset that can be accessed prior to research use. This is not a trivial task but presumably effective and efficient informatics approaches will become commonplace in learning healthcare systems. Further, a simple opt-out system as described will not meet the needs of individuals with low literacy, cognitive or sensory impairments, or language barriers. These circumstances pose obstacles to any form of consent or engagement yet additional thought and resources are needed to address these challenges in this context. Beyond communication and choice for individuals, there are opportunities for transparency and engagement at the institutional level. Increasingly, patients and the lay public are being involved as partners in the design and conduct of research projects and resources such as biobanks.[18] These efforts and expenses are justifiable because they meet the clearly documented expectations of the public for the management of potentially sensitive DAB. Meeting public expectations for transparency and choice will maintain trust in our institutions in this new era of large-scale data and tissue analysis.

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