

Virtual Mentor

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Informed Consent for Biobank-Dependent Research

Commentary by Jeffrey R. Botkin, MD, MPH

Dr. Hundt is a physician at a major research hospital. He is visiting a new patient, Mr. Clifton, who was recently admitted to the hospital for right upper quadrant pain suggestive of gallstones and cholecystitis. Dr. Hundt checks in with the patient to examine him and to explain what the course of hospitalization will be. The patient appears ill, but is alert and oriented. “We will have to draw blood to check some basic labs and to see if you have any possibility of infection,” Dr. Hundt explains. Mr. Clifton nods in understanding.

“I do want to mention to you a program of ours that has been approved by our IRB, which oversees human subjects research,” Dr. Hundt continues. “When obtaining blood samples for labs, we often have leftover blood and tissue. Because we have many researchers studying and developing therapies for genetic diseases, we are attempting to build up our database of genetic material to study population trends and genetic variations of disease. We have therefore established a program for banking leftover blood in our DNA database, in conjunction with basic demographics and medical information obtained from your medical record. We extract the DNA and make the information available to our researchers. Your name and identifying information are removed, and our researchers sign a confidentiality form promising that they will not try to reidentify the source of any genetic specimen.”

“Can you tell me more about what kinds of research the samples are used for?” Mr. Clifton asks.

“The spectrum of research varies across disciplines and disease systems, and the specimens will be used for as-yet-undetermined projects.”

Dr. Hundt gives Mr. Clifton a brochure. As Dr. Hundt is leaving, Mr. Clifton asks if he has to sign anything before the lab comes. “No need, Mr. Clifton. The specimen will be automatically entered into our database without any further action from you,” Dr. Hundt explains. “If you choose not to participate, there is a form at the end of that brochure. Please give that to the phlebotomist and that will let us know not to send your blood to the biobank.”

Commentary

This simple vignette illustrates a surprisingly complicated problem in contemporary biomedical research: should patients be asked to contribute their data and residual tissues to research and, if so, how should they be approached? Biobanks are proliferating and high-volume clinical services are being used as sources of tissues and data for research purposes. Biobanks linked with electronic medical records can be powerful tools for identifying biological correlates of health and disease. Much of the work in this domain is genetic, with the intent to identify DNA-sequence variations associated with disease. But human tissues are potentially valuable for a wide range of studies involving environmental agents, infectious diseases, protein biology, and epigenetic factors. The challenge is how best to acquire large numbers of samples of various types.

A central ethical concern in the conduct of research is the protection of participants from harm. In the biobanking context, there may be harms from the removal of tissues to begin with, such as blood draws or biopsies, but these are usually minor or otherwise justified for clinical purposes. The primary risks associated with this type of research arise from the potential for a breach in privacy to cause stigma or discrimination for the tissue source. Fortunately, to date, there have been no published cases of individual harm arising from biobank-dependent research despite the millions of specimens stored and tens of thousands of studies performed.

So why the controversy? Contemporary concerns fall into at least three domains. First, biobank research is often conducted without the knowledge or consent of those whose tissues are banked. Second, patients and research participants are worried about potential harms from this type of research, and studies show that many want some control over research uses of their tissues. Third, there are potential harms to particular social groups that need to be more fully explored.

The Federal Regulations

The federal regulations governing human subjects research permit research on banked tissues without informed consent in several circumstances. The regulations were established to protect human subjects, defined in the regulations as individuals who interact with investigators or whose identities can be readily ascertained by the investigator [1]. Research using tissues or data that is identifiable is considered human subjects research. Research with tissues or data that are “deidentified” or “anonymized” is not considered human subjects research and therefore can be conducted without oversight from an institutional review board (IRB).

In the case example, Mr. Clifton’s tissue or data can be used by investigators for a wide range of studies without Mr. Clifton’s knowledge or consent as long as the investigators cannot readily determine that the source of the tissue or data is Mr. Clifton. Of course, the tissue donor often gives permission for the original acquisition of the tissues, either through a clinical consent or a research consent process. But subsequent research projects need not re-obtain his consent, even if the research goals are not consistent with the original consent [2]. So if Mr. Clifton

agreed to have his tissues used for research on liver diseases, subsequent use on, say, diabetes research, would be acceptable under the regulations as long as the diabetes investigators could not readily identify Mr. Clifton.

In this regard, the regulations are not consistent with the simple ethical expectation that people live up to their agreements. To the extent that consent forms and processes are explicit about the intended use of the tissues, it is ethically problematic to use the tissues for other purposes, even if the risk to the tissue donor is minimal or nonexistent. There has been an active discussion at the federal level about whether the regulations should be changed to stipulate that uses of tissues and data should be consistent with (or at least not inconsistent with) the informed consent language.

A second scenario in which consent is not necessary is if the IRB waives the requirement for consent. Federal regulations permit a waiver of consent if four criteria are met: (1) the research is deemed to carry minimal risk, (2) the waiver would not adversely affect the rights and welfare of the participants, (3) the research would not be practicable without a waiver, and (4) the research participants will be informed later of the research, when appropriate [3].

In the context of biobank-dependent research, the key criteria are whether the research is considered minimal-risk and whether it is practicable to obtain consent from the tissue sources. As noted, the historical risk associated with this type of research is so low that IRBs often consider it to be minimal-risk unless the information involved is particularly sensitive. IRBs often determine the “practicability” question by the number of tissues involved and the nature of any ongoing connection between the research institution and the tissue sources. If the study involves a small number of identifiable specimens recently acquired from patients in a particular clinic, then the IRB may decide that seeking consent for the new use is feasible and appropriate. If the research is using hundreds of samples acquired over years, then the IRB may determine that it is not practicable to recontact such a large group.

The case example illustrates a situation in which tissues are being acquired for clinical uses but with foreknowledge that any residual tissues will be stored for research purposes. Despite the fact that patients are in the hospital or clinic while the tissues are acquired, an IRB may determine that a detailed research consent process can be waived based on the criteria noted above or decide that a simpler approach, like notification of research use with an opt-out provision, is an acceptable protection of patient autonomy.

The scenario in the case example is entirely consistent with the regulations governing human subjects research. Further, to the extent that a large volume of biomedical research is being conducted on residual clinical tissues without any notification of those whose tissue was used, the notification with an opt-out provision actually meets a higher ethical standard than many programs support. We can hope that clinicians will do a better job than Dr. Hundt of offering a simple

explanation in lay language, but the approach per se is entirely consistent with contemporary regulatory standards.

Public Expectations

The larger problem is that contemporary standards regarding waiver of consent or the use of deidentified specimens is not consistent with what many people want and expect. Those of us in the biomedical research enterprise have good reason to believe that this research is essentially harmless, but members of the general public don't have reasons to believe this or trust us. Further, many people want some level of control over their tissue simply because it is their tissue.

Surveys of the general public consistently show that people want some choice in research uses of residual clinical tissues and aren't supportive of the current lack of transparency [4]. As a concrete example, controversy arose over the research use of residual newborn screening bloodspots in the states of Texas and Minnesota. Privacy advocates became aware that a number of states, including Texas and Minnesota, saved leftover bloodspots following mandatory newborn screening and made these spots available to qualified investigators without the knowledge or consent of parents [5]. Following lawsuits in both states over the lack of parental permission, millions of specimens were destroyed, and both states are moving toward systems that are more transparent with parents.

So there is a mismatch between standards acceptable to investigators (and research oversight systems) and to patients for the perceived risks associated with biobanking and decision making by patients. Investigators are focused on the value of the research and see minimal risks, while patients are concerned about risks and expect to participate in decisions about the use of their tissues.

The other potential mismatch between standards and expectations is in the respective perceptions of "practicability." Many who are not in the biomedical field think it is relatively straightforward to ask people about the management of their tissues. Those on the research side perceive enormous complexities in trying to engage thousands of individuals in a meaningful fashion about relatively complex or abstract decisions. Patients who are sick, anxious, eager to please the doctors, and unschooled in even basic scientific facts and terminology often are not in a position to understand and deliberate about biobanking choices. At best, one might expect the sort of technical and perfunctory presentation by Dr. Hundt in the case example.

From an ethical perspective, the key question is whether individuals are informed about their choices regarding research use of tissues and data and whether they can effectuate a choice without undue burden. In my opinion, whether the approach to choice is an "opt-in" with a signature or an "opt-out" is a secondary issue.

Group Harms and Wrongs

The third set of concerns arises from fears of harm or wrongs to social groups rather than to individual research participants. Let's imagine that all identifiers are stripped

from Mr. Clifton's sample before it is made available for research. The de-identification of the sample significantly reduces or eliminates the risk of harm to Mr. Clifton as an individual. Yet imagine that Mr. Clifton is from a Native American tribe and that his group identification remains with his sample and an investigator wishes to use the specimens from members of his tribe in the biobank to assess historical migration patterns of his tribe across continents. Mr. Clifton might well object to such research because it undermines traditional tribal origin stories. Has Mr. Clifton been harmed by such research? Perhaps not in a tangible way, but we might conclude that he has been wronged, as have other members of his tribe, unwilling participants in research to which they object. This hypothetical scenario is based on the controversy over specimens that were acquired from the Havasupai Indians for diabetes research but subsequently used for a variety of other projects [6].

The federal regulations governing human subjects research were designed to minimize harm to individuals. The regulations do not address the possibility of group harms, although IRBs can set higher standards than the federal regulations and may choose to attend to this potential problem.

Conclusion

Biobanks have become essential tools for contemporary biomedical research. Yet there is clearly much creative work to be done to bridge the divide between patient understanding and expectations and the efficient conduct of research using large sample sets. Earning and maintaining the trust of the public is essential to allow valuable research to move forward.

References

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