

The Use of Human Tissues in Research: What Do We Owe the Research Subjects?

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In the past decade, there have been a number of high-profile legal cases that have involved the removal of human blood samples from the hands of researchers.⁷ In one case, more than 5×10^6 dried blood spots from infants were destroyed after a suit was filed that challenged the state of Texas' right to store infant blood spots for use in future research. In all these cases, there was argument over whether the participants in these research studies had been properly informed about how their samples were going to be used. With the recent publication of *The Immortal Life of Henrietta Lacks* by Rebecca Skloot, about a woman who unknowingly provided the first immortal human cells grown in culture (HeLa cells), the topic of informed consent is now being discussed by book clubs in living rooms and coffee shops across the country.

These cases have raised important questions about the timing and type of consent needed to obtain, store, and use samples for research purposes. To address these questions, we asked the opinions of 4 experts who represent different views on the subject of informed patient consent. David S. Wendler is an advocate for the rights of individuals who contribute to research, Arthur L. Caplan is a bioethicist, Michael Christman is the president and CEO of an independent not-for-profit basic biomedical research institution that maintains a large biorepository, and Jack Moyer, Jr., is a researcher involved with the NIH's National Children's Study.

Should researchers be required to get consent for biological specimens, or are you in favor of a presumed consent with an opt-out option, with the idea that the human tissue is a common heritage of humanity, to be used for the collective good?



Jack Moyer, Jr. (researcher): The concept that human tissue is a shared resource to be used for the collective good is a fascinating notion that deserves further attention. Constructing a framework for the use of biological samples around a common assumption that human tissue is a common heritage of hu-

manity to be used for the collective good might help to prevent disputes regarding both specimens that have been obtained specifically for research and leftover specimens collected for clinical purposes.



David S. Wendler (patient rights): The tissues are not merely "a collective good." The tissues are obtained from specific individuals, and their use involves the interests of the source individuals in at least 4 ways: (1) Obtaining samples can pose risks; (2) future research use of samples can

expose individuals, and the groups to which they belong, to risks; (3) use of samples involves individuals contributing to the research in question; and (4) future research can uncover clinically relevant information about source individuals. Obtaining individuals' consent allows them to decide for themselves whether they face these risks and

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⁷ Recommended references are included in the Data Supplement that accompanies the online version of this Q&A at <http://www.clinchem.org/content/vol57/issue4>.

make these contributions. It also alerts them to the possibility of new information being uncovered.



Arthur L. Caplan (ethics): In my opinion, efforts to secure informed consent for the use of tissue samples and specimens are doomed to failure. Many programs are using open-ended informed-consent forms that are far too vague and incomplete to be valid. Others ask research subjects to waive their commercial interests, but

without knowing the details of what might happen down the road, such blanket waivers are neither binding nor likely to stand up to legal challenges. I think a more appropriate framework is that of altruistic gifting, as is done in many parts of the world with organs and tissues intended for use in transplantation. The donor makes a gift of their organs or of a relative's organs. The gift framework makes it clear that any commercial interest is forgone. It also makes it clear that the use of organs and tissues is open-ended and that possession of specimens has been transferred to a third party for them to control. I think a presumed-consent approach to this type of gift giving makes sense as long as it retains the opportunity for the donor to "opt out" of giving. In addition, even in a gift framework it is important to outline what, if anything, will happen should clinically relevant findings for the donor or donor's biological relatives be found.



Michael Christman (biorepository): Existing specimens that have been anonymized should be eligible for use by researchers without obtaining consent in specific research activities where there is no opportunity to identify the individual from whom the specimen was taken. Although studies using

anonymized existing specimens would typically be exempt from institutional review board (IRB) review, regulatory oversight should be implemented to ensure this condition of use is upheld. However, given advances in genomic technology, anonymized specimens

should not be used in genomic research without consent, due to the potential for identification.

If you feel informed consent is required, what type of consent is best: specific consent, tiered consent, general permission, or other?

Arthur L. Caplan (ethics): Tiered consent (Table 1) that outlines likely uses, disposition of materials over time, policy regarding sale to third parties or transfer of control, and availability of pertinent findings with clinical relevance to donors.

Michael Christman (biorepository): A consent menu with multiple choices. Participant preferences for consent have been explored by Murphy et al., and although there was some support for this consenting menu (10%), most participants preferred blanket consent (48%) or reconsenting at the start of each new research project (42%).

David S. Wendler (patient rights): A good deal of empirical research has been done on individuals' attitudes regarding consent for research on biological samples. These studies consistently find that a significant majority of individuals want to control whether their samples are used for research and that most are willing to contribute samples when asked. The data also show that most people support one-time general consent, on the understanding that future studies will be reviewed and approved by an ethics review committee (e.g., IRB). This consistent and widespread support indicates that one-time general consent offers the choice(s) that most people want to make when deciding whether to donate samples for research. This approach gives those who do not want to contribute their samples, as well as those who would prefer to have more-specific control, the opportunity to decline.

Jack Moye, Jr. (researcher): Specific consent provides assurance that investigators and participants are equal partners in the research enterprise and is readily accomplished when samples are collected for a specific use in a specific project that is accomplished within a relatively specific (short) interval. However, it becomes impractical or irrelevant when samples are banked for long-term storage and uses that have not yet been defined. Most participants in US-based clinical research seem willing to provide samples for future use under a simple general permission.

Do you think research subjects should retain property rights to their specimens? Should they share in any potential financial gain?

David S. Wendler (patient rights): As a general principle, individuals should share in the beneficial results

Table 1. Approaches to informed consent for research on stored biospecimens.

Approach	How consent is obtained
Specific consent	Research participants are recontacted and asked to consent for each new use of their specimen or for information that is outside the scope of their original consent.
Tiered consent	At the time samples are collected, research participants are presented with a menu of options from which to choose, which may include general permission for future use, consent only for future uses, related to the original study topic, consent for future uses unrelated to the original study topic, and specification that the investigators must obtain specific consent for any future use that differs from the original study.
General permission	At the time samples are collected, research participants are asked to permit all future uses that a qualified ethical review board determines to be scientifically meritorious and ethically defensible.
Presumed consent	At the time samples are collected, research participants are informed that their specimens will be used in future research unless they expressly deny permission.

Reprinted with permission from: Mello MM, Wolf LE. The Havasupai Indian tribe case: lessons for research involving stored biologic samples. *New Engl J Med* 2010;363:204–7.

of the projects to which they contribute. Indeed, on standard accounts, failing to provide individuals with a fair level of benefits is a paradigm case of exploitation. The fact that providing samples involves an important contribution on the part of source individuals suggests that they should, as a matter of fairness, share in the benefits, including financial gain, of research projects. However, putting this principle into practice is, at best, enormously complicated. In practice, it is rarely clear what constitutes a fair level of benefits or how investigators might provide benefits to individuals, including those who provided samples decades previously, as well as samples that have been anonymized. Given these concerns, it is not surprising that some would rather imagine that sources have no claims in this regard.

Michael Christman (biorepository): I think that participants should be informed, as part of the consent process, about their property rights as well as the investigator's potential for financial gain and whether they, as the participants, will share in any financial gain. Provided the participant is made aware of these conditions before enrollment in the study and that they have the option to consent or decline participation on the basis of this information, either allowing for or disallowing property rights and financial gain should be acceptable. In cases where participants will not retain property rights or where there is the expectation of financial gain on the part of the investigator, consent should not be waived.

Jack Moye, Jr. (researcher): Unless research is undertaken with the specific objective of developing a commercial product, it seems difficult to assert a proprietary interest in research on the part of tissue donors. Assertions of property rights to samples in cases where the issue has been litigated generally correspond with perceived value and arise after the fact. It's hard to put a value on something that doesn't yet exist.

Curiously, there's an asymmetry in how we treat the "property rights" of samples compared with how we treat data. Increasingly, study participants are given the option to direct the use of their samples, including invoking the destruction of stored material. In contrast, if a participant discontinues their involvement with a study, their previously collected data are retained and often continue to be used for many years.

Do you think that making specimens deidentified really alleviates risk and ethical obligations to the research subject?

Michael Christman (biorepository): In the era of dense genome sequencing there is really no such thing as a truly deidentified sample. If a researcher were to generate sequence information on a tissue sample and place that information in the public domain, the original donor would, in principle, be able to uniquely identify their own sequence, using the results of relatively inexpensive commercially available genetic testing. A fishing expedition to try to identify one's public sequence could result in the donor learning information that they were not prepared to learn—such as their Alzheimer's risk or Huntington's disease status. In addition to the risk of the specimen donor identifying their own sequence, the sequence could be identified by others, including researchers, government or law enforcement, or family members. This risk was acknowledged by dbGaP, prompting the NIH to update their GWAS data-access policy in 2008.

Arthur L. Caplan (ethics): Deidentification helps a great deal. Although it is possible to track back and decode the identity of sources, the deidentification process makes it clear that privacy and confidentiality are the expected moral framework for those giving tissues or data to biorepositories. I think the creation of criteria to establish what entities can serve as trusted

third parties to hold linking identification data to sources ought to be a top priority for biobanks, regulators, and patient groups.

What entities do you think should serve as trusted third parties to hold linking identification data?

Arthur L. Caplan (ethics): There are two challenges that must be met in creating trusted third parties to hold information capable of being used to link to specific research subjects retrospectively.

First, criteria must be laid out that make it clear that transparency will guide decisions. This means that while confidentiality and privacy should never be breached, the trusted entity must always provide a public rationale for decisions to link or not link data in databases to clinical or diagnostic information. This publicity affords parties the chance to appeal decisions and at the same time to offer some form of public notice to those who might benefit by an effort to link to anonymized information.

Secondly, trusted third-party entities must have at least one community member or patient representative. Ideally, this would mean using advisory groups that combine scientific expertise, such as a subcommittee appointed by a professional society in collaboration with one or more patient-advocacy groups. Government agencies or legislatures could appoint such groups and charge them with the duty to protect the public interest and the health of both the public and vulnerable parties such as children, the mentally incapacitated, and prisoners.

Trusted third-party entities should be not-for-profit groups so that their decisions can be made independently of commercial interests. It is essential that those given the key to the “lockbox” of genetic data be able to secure the trust of both affected parties and the general public. Their membership and operational structure should reflect the need to maintain that trust.

Do you feel that the consent process should be different if the researchers are accessing and using genetic information?

Michael Christman (biorepository): Yes. Every tissue sample in which sequence information is generated and placed in the public domain is potentially identifiable by the donor if they have a limited set of genetic testing done (say at a direct-to-consumer testing company). Thus, it is important to prepare tissue donors for the possibility of their finding out a lot of genetic information about themselves. They would have to seek out this information, but it will become increasingly easy to do so.

Jack Moye, Jr. (researcher): Treating any particular category of information as exceptional may be well in-

tended but in my view is misguided. *All* individually identifiable information in medical care and clinical research should be afforded equal and effective protection. Examples abound of information items that are potentially harmful in medical care and clinical research—genetic information is only one. We’ve experienced a quarter century of HIV exceptionalism, some of which—perhaps much of which—appears to have contributed to the spread of the epidemic. I think repeating that experience with genetic information would be a mistake.

What do you see in the future for the regulations governing the use of human tissues?

Arthur L. Caplan (ethics): The evolution of biobanking means more mergers and acquisitions and combining of data sets, which, sadly, portend more legal fights to come. On a happier note, I think rules to permit retrospective use of existing specimens and data will evolve as trusted third-party entities emerge that can act as ethics committees to give surrogate consent to the use of these materials and data for biobanking studies.

Michael Christman (biorepository): Electronic re-consent will become an effective mechanism to inform tissue donors of potential new uses for their material. This has not existed historically and should make previously unanticipated specific consents possible logistically. The use of human tissues and biological specimens in combination with technological advances has outpaced regulation. Revision and standardization are needed for current regulations, which, in light of the identifiable nature of genetic information, are outdated. In addition, regulations that clarify sample ownership and establish guidelines for participant and researcher financial gain would benefit researchers, participants, and institutions.

David S. Wendler (patient rights): With respect to patient protections, one of the most important issues is the extent to which individuals should be provided with information of the results from research using their samples. It is not clear that this can be addressed appropriately in regulations, but guidance would be very welcome.

Jack Moye, Jr. (researcher): I suspect that there will be a move away from specific consent toward a more uniform simplified and standardized consent, along the lines of tiered consents. Disputes arising out of unresolved issues about property interests in samples will be exacerbated by increasing commercial interests in research development. Informatics solutions will provide increasingly inventive ways to challenge the existing

paradigm for what constitutes “research involving human subjects” when it comes to research involving biological samples. Unintended missteps in use of genetic information in research will provoke calls for increasing regulation over use of genetic information.

Ann M. Gronowski: Interestingly, despite the varied backgrounds of these 4 experts, their opinions have much in common. All feel that protection of research participant privacy and confidentiality is of the utmost importance. In cases in which individual sample data can be linked back to the patient, research participants should be asked to give consent, and genetic information should be viewed as linkable. All would also agree that as we move into the future, more guidance is needed for researchers on how to properly obtain consent and protect participants in research studies.

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