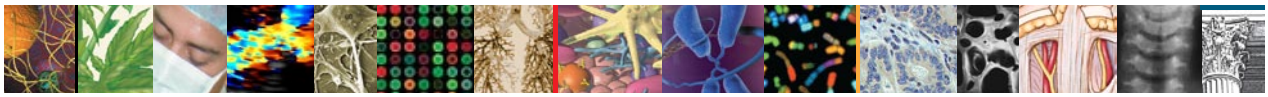

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Perspective

The Havasupai Indian Tribe Case — Lessons for Research Involving Stored Biologic Samples

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On April 20, 2010, Arizona State University (ASU) agreed to pay $700,000 to 41 members of the Havasupai Indian tribe to settle legal claims that university researchers improperly used tribe members' blood samples in genetic research.[1] The settlement closes a difficult chapter for both parties but leaves open a bedeviling question for genetic research: What constitutes adequate informed consent for biospecimens collected for research to be stored and used in future, possibly unrelated studies? The case illuminates the clashing values that have driven debate in this area and the importance of understanding the study population's perspectives.

The Havasupai suit stemmed from a 1990 diabetes study in which ASU researchers collected more than 200 blood samples from tribe members. The consent form described the project as studying "the causes of behavioral/medical disorders," but prestudy communications with tribal leaders apparently focused on diabetes. The researchers used the samples in multiple studies unrelated to diabetes, sharing them with other investigators. Tribe members particularly objected to three uses: a study evaluating the genetic basis of schizophrenia, which could stigmatize the tribe; one examining inbreeding, which raised stigmatization issues and concern related to a cultural belief that inbreeding brings harm to one's family; and evolutionary-genetics studies suggesting that contrary to the tribe's origin story, its ancestors migrated across the Bering Sea.

In 2004, tribe members filed a $50 million lawsuit alleging, among other things, fraud, breach of fiduciary duty, negligence, and trespass.[2] The core legal question was whether the downstream uses of the samples fell within the scope of the donors' informed consent. The Havasupai faced an uphill battle, since other plaintiffs who have asserted their rights to control the use of research specimens have generally been unsuccessful.[3]

However, after several years of legal wrangling, ASU agreed to settle. In addition to providing monetary compensation, ASU formally apologized and agreed to work with the tribe on issues of health, education, and economic development.[1] ASU also agreed to return the remaining samples to the tribe. Although the settlement sets no formal legal precedent, the university's public acknowledgment of wrongdoing is

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.

important symbolically and could affect prospective plaintiffs' and attorneys' views of litigation opportunities.

Case law is fairly clear that biospecimen donors do not retain property interests in samples collected and used in accordance with properly obtained informed consent. However, what constitutes adequate informed consent is unsettled. Federal regulations require informed consent when identifiable biospecimens are collected for research purposes, but such regulations provide little guidance on how to obtain informed consent for future, unspecified uses.

Research on previously collected biospecimens is permitted without obtaining new informed consent when samples cannot be traced back to individuals or when the research presents only minimal risk to participants, does not adversely affect their rights or welfare, could not practicably be carried out if new consent were required, and provides a mechanism for giving participants additional pertinent information after participation when appropriate. But institutional review boards (IRBs) have considerable discretion in interpreting these rules and must reconcile them with guidance from the Office for Human Research Protections, which states that informed consent for storing identifiable biospecimens should include a clear description of "the specific types of research to be conducted." Consequently, what constitutes adequate informed consent for research on stored samples is as much the province of ethical deliberation as law.

Various expert groups have considered ethical issues regarding research on stored biospecimens and suggested approaches to obtaining informed consent (see Table 1). Two key issues remain contested. The first is whether general permission, sometimes called blanket or global consent, for future research uses constitutes meaningful informed consent. Some argue that such consent is not informed because without knowing the nature of the studies, one cannot evaluate the risks and benefits of participation. Others respond that the risks are negligible. Although there is some risk that detailed genomic data can be used to identify individuals, the primary risk is an inadvertent breach of confidentiality that results in adverse consequences. That risk can be minimized by labeling samples with code numbers and storing links to identifying information separately.

The second issue is whether removing donors' identifying information from samples ("anonymizing" them) eliminates the ethical dilemma. Federal regulations stipulate that samples that are not individually identifiable do not trigger legal obligations to obtain informed consent or even to seek IRB review. The rationale is presumably that analysis of such samples does not involve risk to contributors. But is risk the only relevant consideration?

An alternative perspective is that people have a right to control the uses to which their bodily tissues are put, regardless of whether those uses pose any risk. In this view, the donation of biospecimens for research involves a compact in which the participant agrees to donate samples and the researcher agrees to abide by certain conditions regarding their collection and use. Allowing donors to grant general permission is ethically acceptable, but the use of even anonymized specimens for purposes beyond the agreed uses is not, unless the researcher seeks consent for the new uses.

The Havasupai plaintiffs' claims reflect this view. Tribe members contended that they would not have contributed samples for the non-diabetes studies, which they found offensive. Anonymizing the samples would not have eliminated their objections.

Consideration of best practices for informed consent should begin with a determination of what

Table 2. Advantages and Disadvantages of Informed-Consent Approaches.

Approach	Advantages	Disadvantages
Specific consent	Offers participants the most control over specimen use Provides the most information with which to evaluate risks and benefits of study participation Allows participants to reconsider their willingness to participate in light of new scientific developments	May be highly burdensome and costly for researchers May result in loss of research opportunities if recontacting participants is impracticable Involves some loss of data due to participants' refusal to consent and researchers' inability to locate participants Burdens participants with repeated requests from researchers
Tiered consent	Offers participants a reasonable degree of control over specimen use Allows the majority of participants who find general permission acceptable to express this view Reduces the burden on researchers, as compared with specific consent Enables participants to avoid being recontacted if they so wish	Retains the disadvantages of specific consent and general permission for participants selecting those options Provides less latitude than specific consent for participants to reconsider their willingness to participate in light of new scientific developments May make consent forms too complex Involves some loss of data owing to refusal to consent, as compared with general permission and presumed consent
General permission	Facilitates extensive scientific use of biospecimens at low cost Avoids loss of data for future studies due to inability to obtain new consent Minimizes burden on researchers Enables participants to avoid being recontacted if they so wish	Offers participants limited control over specimen use Risks loss of data of participants who would consent to some, but not all, future uses Provides no specific information about the risks of future studies, making consent less than fully informed Provides no opportunity for participants to reconsider their willingness to participate in light of new scientific developments
Presumed consent	Maximizes the scientific use of biospecimens at the lowest cost Avoids loss of data for future studies due to inability to obtain new consent Minimizes burden on researchers Enables participants to avoid being recontacted if they so wish	Offers participants the least control over specimen use Burdens participants with having to affirmatively act to prevent future use of specimens Retains the other disadvantages of general permission

research participants want. Multiple studies have explored participants' preferences, at least in the United States and Europe, and have shown that a majority of the public finds general permission acceptable; however, a sizable minority prefers to be asked for specific consent for new uses.[4,5] Some uses, such as cloning and research on potentially stigmatizing traits, heighten donors' concerns about use of their biospecimens. For many participants, these preferences don't change if samples are anonymized. These findings suggest that at least some participants consider factors other than individual risk when evaluating future uses of their specimens.

Each approach to informed consent has shortcomings (see Table 2), but we believe that tiered consent strikes the best balance between respecting participants and providing opportunities to advance science. As the Havasupai case shows, general permission can lead to problems, because participants may not contemplate all possible future uses. Specific consent is ethically appealing but involves considerable burdens for investigators and participants. It may result in attrition among participants and loss of valuable research opportunities. Tiered consent does not avoid such problems, but it limits them to the minority of participants who feel strongly about their right to control their samples. And though it doesn't circumvent the core question of whether blanket consent is really informed consent, it allows participants to narrow their permission for future uses if they wish (see box).

The Havasupai case illustrates the problems of considering new uses of stored biospecimens only through the lens of potential risks to individual contributors. The desire of participants to control the use of their biospecimens also has moral significance, as does a community's stake in research that may affect its collective interests. These considerations should be reflected in informed-consent practices.

Despite its lack of precedential value, the Havasupai case settlement may lead to changes in research practices. It suggests that researchers need to ensure that the study population's perspectives are understood and considered. When research involves a defined community, community consultation during study planning can help to identify areas of concern regarding possible fu-

Example of Language for Tiered Consent.*

With your permission, we would like to store your blood sample for use in future research. You do not have to agree to this in order to be in the study, and your decision will not affect the care you receive from the study doctors.

Please pick one of the choices below:

- My blood may be kept and used in research to learn about, prevent, or treat diabetes.
- My blood may be kept and used in research to learn about, prevent, or treat diabetes or other health problems (e.g., heart disease and mental illness).
- My blood may not be used in future research unless researchers contact me to tell me about the study and ask my permission.
- My blood may not be used in future research. I do not want researchers to contact me about future studies.

* Adapted from the National Cancer Institute's informed consent template for cancer treatment trials.

ture uses of biospecimens so that tiered-consent options reflect what matters to study participants. Although future research directions are not usually known, consultation can help in identifying sensitive topics and evaluating the need for ongoing partnership with community representatives.

The storage and ongoing research use of biospecimens have long raised troubling questions about informed consent. Although practices have evolved considerably, conflicts such as the Havasupai case suggest they have not yet fully risen to the ethical challenges of the genomic age.

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