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Genomic Justice for Native Americans: Impact of the Havasupai Case on Genetic Research

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Abstract

In 2004, the Havasupai Tribe filed a lawsuit against the Arizona Board of Regents and Arizona State University (ASU) researchers upon discovering their DNA samples, initially collected for genetic studies on type 2 diabetes, had been used in several other genetic studies. The lawsuit reached a settlement in April 2010 that included monetary compensation and return of DNA samples to the Havasupai but left no legal precedent for researchers. Through semistructured interviews, institutional review board (IRB) chairs and human genetics researchers at US research institutions revealed their perspectives on the Havasupai lawsuit. For interviewees, the suit drew attention to indigenous concerns over genetic studies and increased their awareness of indigenous views. However, interviewees perceived no direct impact from the Havasupai case on their work; if they did, it was the perceived need to safeguard themselves by obtaining broad consent or shying away from research with indigenous communities altogether, raising important questions of justice for indigenous and minority participants. If researchers and IRBs do not change their practices in light of this case, these populations will likely continue to be excluded from a majority of research studies and left with less access to resources and potential benefit from genetic research participation.

Keywords

ethics; justice; inequality; protest; other

Introduction

The Havasupai Tribe Files Suit over Misuse of DNA

In 2003, Carletta Tilousi, a member of the Havasupai Tribe of northern Arizona, discovered that DNA samples she had donated for a genetic research project on type 2 diabetes in 1989 were in fact being used in nondiabetes-related genetic studies by researchers at Arizona State University (ASU). In Ms. Tilousi's view, she had not provided consent for any studies

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beyond the original diabetes-related research (Bommersbach 2008; Rubin 2004). On further investigation, Ms. Tilousi learned that the DNA samples that she and other members of the Havasupai tribe had donated had been used for studies on schizophrenia, ethnic migration, and population inbreeding, all of which are highly charged topics that are taboo in the Havasupai culture (Bommersbach 2008; Rubin 2004). The Havasupai Tribe filed a lawsuit against the Arizona Board of Regents in 2004 over the misuse of their genetic samples and lack of complete informed consent involved in the samples' collection (*Havasupai Tribe of the Havasupai Reservation v. Arizona Board of Regents and Therese Ann Markow* 2009; Hart and Sobraske 2003). The case was an important challenge to the definition and use of "informed consent," particularly with vulnerable populations. This research begins with the outcome of this court case and examines how institutional review board (IRB) officials understand the significance of this case and its implications for how they conceptualize and enact human subject protections. This analysis leads us to examine how researchers and IRBs adapt to new situations, particularly with genetics research and informed consent.

Between 1990 and 1994, DNA samples were solicited from approximately 400 Havasupai tribe members in conjunction with the Diabetes Project led by researchers at ASU. The stated intent of the project was to understand why more than half of Havasupai adults suffered from type 2 diabetes (Bommersbach 2008). The Havasupai, a small, isolated tribe living in a remote part of the Grand Canyon, had limited access to fresh food and health care. The Diabetes Project included education about diabetes, the collection and testing of blood samples, and genetic association testing. To obtain informed consent, ASU researchers made oral statements recruiting the tribal members to the research study. When they agreed, participants were asked to sign informed consent documents written in English (Hart and Sobraske 2003). Although the consent form said that the samples would be used for research on "behavioral/medical problems," tribe members were told that their samples would be used specifically for genetic studies on diabetes (Bommersbach 2008; Hart and Sobraske 2003).

However, initial studies failed to find a genetic link with type 2 diabetes. The samples were stored, and subsequently used in other ongoing genetic studies and distributed to researchers for unrelated studies. The researchers obtained IRB approval from ASU for studies on diabetes and schizophrenia; however, Havasupai participants alleged that researchers had failed to make clear that the samples may be used for studies on schizophrenia and that no expanded informed consent was sought. Since mental illness is highly stigmatized in the Havasupai culture, tribe members asserted that they would not have consented to such research had they been properly informed (Bommersbach 2008; Hart and Sobraske 2003). The tribe also alleged that researchers gained illegal access to Havasupai medical records by entering the local medical clinic and removing secured files without permission from tribal officials or clinic administrators (Hart and Sobraske 2003).

In April 2010, the *Havasupai Tribe v. Arizona Board of Regents* case reached a settlement in the tribe's favor: tribe members received $700,000 in direct compensation, funds for a tribal clinic and school and, most significantly from the standpoint of several tribe members, the return of the tribe's DNA samples (Harmon 2010b; Mello and Wolf 2010). The settlement

signified closure for tribe members, and they took the DNA samples home to properly dispose of them in a culturally appropriate ceremony (Harmon 2010b).

The return of DNA samples was a significant moment for the Havasupai Tribe because DNA and biological materials are sacred to many Native Americans, as eloquently described by the late Hopi geneticist, Dr. Frank Dukepoo, who said,

> To us, any part of ourselves is sacred. Scientists say it's just DNA. For an Indian, it is not just DNA, it's part of a person, it is sacred, with deep religious significance. It is part of the essence of a person (Petit 1998).

Many Native Americans view DNA as a valuable part of one's personhood, not as a material object. However, in the contemporary US research context, DNA samples are generally considered the property of the research institution once they are obtained and researchers almost never return biological material to participants (*Washington University v. Catalona* 2007). The return of the Havasupai samples meant the end of all future studies with those samples and challenged the long held notions of ownership surrounding DNA samples contributed to research (Arbour and Cook 2006; Wiwchar 2004).

The Impact of the Havasupai Case on Genetic Research in the United States

The effect of the Havasupai case on many native tribes was clear. The events surrounding ASU's research on the Havasupai distilled existing distrust of medical researchers and discouraged tribe members from participating in further research, even that which might benefit the tribe (Bowekaty and Davis 2003; Boyer et al. 2011; Harmon 2010a; AJMG 2010). In May 2003, the Havasupai Tribe issued a "Banishment Order" barring all ASU researchers and employees from the Havasupai reservation and halting all research (Bommersbach 2008). The Inter Tribal Council of Arizona and the National Congress of American Indians each passed resolutions supporting the Havasupai Tribe (Beard 2006; NCAI 2006). For independent reasons and based on historical issues of distrust and lack of return of results, in 2002 the Navajo Nation passed a moratorium on genetic research within their boundaries. The Havasupai lawsuit raised several new questions for the Navajo Nation and other tribes. The lawsuit revealed not only distrust in outside medical researchers but also several claims of injustice: harm and lack of human subject protection, the unequal distribution of "benefits" from participating in research, and questions of community exploitation by researchers. In doing so, the lawsuit has made tribes reluctant to alter research policies, and the moratorium remains in effect in 2012 (McCabe and McCabe 2008; Brown 2002; NNC 2002). As a consequence of the Havasupai case and prior instances of genetic research injustices, many tribes continue to refuse participation in genetic research despite researchers' ongoing efforts to recruit them (Harry, Howard, and Shelton 2000; Santos 2008; Bommersbach 2008).

The effect on the scientific, research communities, however, is largely unknown. Because the case was never tried in court, the Havasupai settlement left no formal legal precedent for changes in informed consent procedures, recommendations on secondary uses of samples, or considerations for vulnerable populations in research. Researchers and oversight boards, such as IRBs, were given no clear guidance on what changes should be made to existing procedures. But the Havasupai case challenges notions of informed consent, particularly

with vulnerable populations, by signaling that broad consent forms and incomplete disclosure did not bring about the full understanding of research participation necessary for truly informed consent. When the case settled, it was covered in numerous scientific publications including *Nature* magazine (Dalton 2004) and the *New England Journal of Medicine* (Mello and Wolf 2010), in addition to appearing on the front page of the *New York Times* (Harmon 2010b) and in *Phoenix Magazine* (Bommersbach 2008).

The case raised issues of just and respectful research practices involving indigenous people. In particular, it highlighted the effects of research harms on the community, challenged the appropriateness of certain types of research, and questioned the adequacy of informed consent (Santos 2008). Yet several questions remain: what is just research, by whom and from whose perspective is justice determined, and how might research be conducted in a more just manner? Commentators suggest that researchers need to be more careful about working with research participants and indigenous communities due to perceived lack of trust, reciprocity, and respect (Mello and Wolf 2010; Santos 2008). Until now, however, very little work has been done to examine whether and how researchers and IRBs understand that their expertise has been challenged and, further, whether this challenge has altered their notions of human subjects' protection and their practices of implementing just research practices. The specific implications of this case on the conduct of genetic researchers and IRBs in the United States have not been thoroughly explored. As such, the broader impact of the lawsuit on biomedical research remains largely unknown.

Through interviews with US researchers and IRB chairpersons, this article examines the ways researchers and IRB experts think about and implement informed consent practices in research studies, particularly in light of the Havasupai case settlement. In particular, we focus on the silence around justice and equity in genetic research involving indigenous populations. The results reveal important shifts in attitudes about science and informed consent in the context of genomics research, but they do not reveal how to address unique cultural concerns of indigenous communities. We also explore responses to the Havasupai case as understood by the researchers and IRB chairs; respondents here reported concerns with the lawsuit and protecting human subjects through the informed consent process. By only addressing consent and not cultural concerns, research will fail to achieve justice for those communities participating in research. These concerns must be addressed in order to facilitate indigenous participation in research and promote fair and just distribution of research benefits (Burke et al. 2011; Cochran et al. 2008). IRBs follow human subjects' regulations to ensure that requirements are met regarding minimal risk, informed consent, and participant confidentiality. However, there appears to be a constant "slippage between norms and practices" when IRBs generally fail to take a step further to ensure just and equitable research inclusion across all populations (Jasanoff 2005).

Materials and Methods

The study population consists of IRB chairpersons and biomedical faculty researchers engaged in human genetic research at six top National Institutes of Health (NIH)-funded medical schools across the United States, as identified by the 2009 ranking tables based on data reported by the NIH (Blue Ridge Institute for Medical Research 2009). This sampling

method assumes, based on NIH-funding priorities and the elevated availability of resources, that the level of funding corresponds to a larger number of biomedical researchers doing human genetics research in those institutions than at institutions receiving less NIH funding.

Candidates were identified for recruitment if they were (1) IRB chairs listed on an IRB roster at one of the six institutions or (2) listed in the results of a search for individual researchers through each institution's website using the following search terms: human, genetic, sample, DNA, and population. These individuals were contacted by e-mail and invited to share their perspectives on informed consent practices, the use of human genetic samples in research studies, and the impact of the lawsuit involving the Havasupai Tribe and ASU. A total of twenty-three interviews were conducted with eleven IRB chairpersons and twelve human genetics researchers who were faculty members in departments of Genetics, Medicine, Biochemistry, Biology, and Nursing.

Interviews were conducted with a semistructured interview guide that included questions about their involvement in genetic research (Researcher) or protocol review (IRB chairperson), thoughts on the Havasupai case, and general reflections on the informed consent process. For example, researchers were asked, Has the Havasupai case affected your research? IRB chairpersons were asked, Has the Havasupai case affected the way you review research protocols? Both groups were asked more broadly, What are your thoughts on informed consent? with follow-up questions on specific types of consent issues such as on consent for broad uses of samples.

Interviews were conducted upon the consent of the participant. Identifiers were removed to maintain the privacy and confidentiality of each respondent. All interviews were recorded, transcribed, and independently checked for accuracy. Codes were created from the transcripts and, using NVivo 9 qualitative data analysis software, data were iteratively coded. Recurring themes were identified from the coding scheme through conceptual connections within and across the identified codes. A second researcher trained in qualitative research methods independently coded a 15 percent sample of the interviews, achieving a Cohen's κ statistic of .81. Data on the statements relevant to perceptions and impact of the Havasupai case are reported here as "Researcher" or "IRB chair" followed by the interview number (Int#).

Results

A Challenge to IRB Practices

Most researchers and IRB chairs either reported hearing about the case through the *New York Times* article or could not remember the exact news source from which they learned of it. Some also alluded to institutional discussions and mentions of the case at national meetings. Knowledge of the case ranged from limited (i.e., not being able to remember the tribe name, the correct researcher institution, or that the case resulted in a settlement) to extensive (i.e., knowing the case complaints, the issues that were raised, and the settlement terms). Those who knew more about the case tended to know someone personally who had used the Havasupai samples in their own work and been forced to return the DNA or were

themselves researchers who worked closely with tribes or other small, isolated populations. In all, the challenge to research practices went largely unnoticed.

The informed consent form used in the original Havasupai sample collection was not made publicly available, so interviewees had no way to assess the thoroughness and adequacy of the informed consent process. Some respondents defended the investigators at ASU, saying the informed consent form may have been adequate, and one researcher thought the consent forms may have been "sufficiently broad" (Researcher Int11) to allow them to carry out additional studies unrelated to diabetes. Others gave the benefit of the doubt to the ASU researchers, and found ways to explain why the secondary studies were done, but did not know details about the informed consent forms or the process:

> I am sure [the ASU researchers] have defenses and I am sure that maybe what they were doing was, at the time, being done all the time. But, once you call them on it and look at it, it really was not very defensible, I think. (Researcher Int5)

Another was unsure of the details but stated that it certainly did raise awareness of issues in informed consent:

> I'm not necessarily stating that there should have been sanctions. I think it does serve as a wake-up call, probably to both investigators and IRBs that they be a little more careful and more specific as to what they say they're going to do and what they do do, and certainly can put blame on both parties. Not criminal blame, again I don't think anybody did anything illegal but bordering on unethical. (Researcher Int11)

Both researchers here distanced themselves from the case and hesitated to place blame on any particular party. However, they both suggested that there might have been reasons for carrying out secondary studies with the Havasupai samples that were in line with standard practice at the time. Yet, in retrospect they are willing to say that those standards and consequent behaviors are "not defensible" and even possibly "unethical."

Although the case served as a "wake-up call" for some respondents, many researchers interviewed tended to think that the case had not and would not affect them directly. This sentiment was usually expressed because the researcher did not work with indigenous or small populations.

> Interviewer: Do you think it has affected your research or the way you think about informed consent issues?
>
> Researcher Int15: Um, no. [Long pause, laugh]
>
> Interviewer: Why not? [Laugh]
>
> Researcher Int15: I think we were pretty rigorous about our informed consent to begin with, and I think we've thought about, you know, we, I personally have not done anything with really small populations.

Many researchers emphasized that they were not working with tribes or minority populations and had not used samples for studies that were not approved by their IRBs. Interestingly, they did not seem to take any generalizable lessons from the Havasupai case

such as traditional ethical considerations about how DNA samples in general should be used and that these considerations may exist independently of specific consent requirements. For researchers in this study, the Havasupai case did not appear to pose a threat because other factors, such as the increasing rigor of informed consent requirements and not working with small, isolated populations, affected their perceptions of the relevancy of the case.

Similar to academic researchers, many IRB chairs also did not feel directly affected by the Havasupai case. Rather, they were concerned with other issues around informed consent documents and the notion of time that has elapsed since the beginning of the Havasupai study:

> I'm concerned when these are adjudicated in the court 'cause it's never quite clear what could the investigators have done differently. They got all the approvals, they got the consent form, and then somebody some number of years later say, "Well that, sorry, we didn't think that was good enough." So, it's just a challenging thing for the IRB and for the investigators to deal with. (IRB chair Int6)

IRB chairs showed more concern than researchers about ensuring that informed consent forms were worded in a way that protected the participant, the researcher, and the institution. Here, the IRB chair is worried about changing norms of research ethics; a protocol that was "good enough" (for IRB approval) at one point in time might not be "good enough" years later and therefore at risk of a lawsuit. In discussing the Havasupai case, respondents worried about how science has changed over time and that old informed consent may not adequately cover all proposed new uses of DNA. This notion of time pervades other themes in this study. IRB experts rely upon the standardization of their practices to determine whether ethical conduct has been maintained from the beginning of a study to the present. In this case, ethical standards were met if the institutional requirements were also met. However, just and equitable research inclusion cannot be achieved if we do not address the main cultural concerns of smaller populations that deter them from participation in research. The Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978) highlights justice as an important principle for research with human participants: but researchers and IRBs fell silent on the acts of injustice and unfair research with the Havasupai. Rather, the principle of autonomy carries greater weight here in ensuring that individual research participants give their informed consent, but it does not fully address potential issues or concerns of a group or tribe. In short, a "one size" informed consent form does not fit all persons for all time.

Valuing DNA

As discussed, the settlement terms in the Havasupai case included the return of "valuable" DNA samples to the research participants, an act that very rarely occurs in genetic research in the United States. In this study, value is construed as a material (DNA) that carries value for researchers; they study the DNA to make important discoveries, publish the findings, and advance their careers, all of which brings financial gain and recognition. The return of DNA samples is of great significance because it challenges notions of biomaterial ownership in research and what constitutes value and for whom. DNA is essential to genetic research: samples are typically banked or kept in laboratory freezers, sometimes for decades, and used

for multiple studies across many years. Researchers value the ability to use these samples to study disease association, population substructure, evolutionary history, and other biomedical studies. Fewer restrictions on sample usage allow researchers to stretch their research dollars using samples for multiple studies. One IRB chairperson recognized the uniqueness of DNA compared to other biological materials and the need to treat it differently:

> Research on DNA is different than other kinds of research and probably has sensitivities that need to be … taken into account. (IRB chair Int3)

In particular, older samples were singled out as being very valuable for scientists because they aid in understanding human evolution and provide material for multiple types of biomedical studies:

> These samples can be very valuable. Particularly older samples can be exceptionally valuable because they can give you a window into how things have evolved, both from a clinical point of view or just from basically an evolutionary historical point of view. And so sometimes these older samples are really the most valuable scientific tools. (Researcher Int17)

But despite their value, older samples pose challenging questions because it is impossible to go back to obtain new samples or replenish existing samples from the same individuals or population under the old collection criteria. Researchers and IRB chairs have raised questions about what type of informed consent was given originally and what research subjects understood at the time of DNA sample collection. In many cases, individuals may no longer be living. The same researcher continues with a new dilemma:

> But then, you know, because they were old, they were collected when informed consent was different than it is in it's current form. Then you have the dilemma, that the informed consent at that time covered the study that you're trying to do now. (Researcher Int17)

Because of the problems with older informed consent procedures, especially in cases where the researchers who collected the samples were unable to predict or disclose all potential future uses, it is unclear to many researchers whether it is acceptable to use old samples for new studies. Issues with older samples arise because of changes in informed consent standards; they become too valuable to discard, but practically unusable because they do not meet the new standards of consent.

Science is constantly changing, so informed consent must change with it. However, it is difficult to predict the studies that one can do with old samples that exist today, as described by one researcher:

> And, that's where I think most of the evolution of the informed consent has gone, is how do you deal with the dynamic nature of science? And it's a difficult one because like I say we can't really foresee what we can do with the sample now versus what we can do with it 10 years from now. (Researcher Int17)

This burdensome and confusing issue in dealing with old samples puts some researchers and IRB chairs in a complicated situation: do they hold onto the samples and apply the standards

of informed consent today, or do they apply the standards from the time the samples were collected? And, would secondary uses of old samples undermine the expectation that research participants had for what studies would be performed with their samples?

Before gene sequencing technologies were available, a relatively small number of genetic studies had the ability to use older samples and so informed consent procedures were less stringent and codified. Older consent forms could not have predicted the development of new technologies, and so it was impossible to obtain full informed consent for future research involving such new technologies as genome sequencing. Nonetheless, over time researchers have shared these samples with others in their labs, their collaborators, or passed them on as legacy collections to young investigators who are starting their research careers. As one researcher noted, these collections pose a new challenge as they have been passed down from one researcher to another enough times that the original collection process is unclear:

> The huge remaining problems are the legacy collections that are scientifically incredibly valuable and were just consented really lousily. (Researcher Int5)

Researchers do not want to dispose of the samples, knowing they could potentially be very valuable to future research, but there is concern about what new research should be allowed with old samples, especially when there is no confidence that proper informed consent was obtained at the outset.

It is difficult to predict how research participants in these older collection efforts would respond to the broader uses of old DNA samples today, especially since technological advances have allowed researchers to do more with samples than they were able to do previously.

> It’s important to be able to access specimens that were previously collected. Genomics is the perfect example, in that many of these samples were collected long before we realized that we would be able to, you know, easily sequence the entire genome. (IRB chair Int19)

Some IRB chairs found it difficult to interpret broad consent forms that were collected in the past when both researchers and participants could not predict or comprehend all the potential future uses. One researcher made an attempt to resolve this dilemma by seeking broad consent from present-day research participants:

> So, whenever I’ve done consent, I’ve tried to consent people extremely broadly knowing that the appetite for data and for science is very large. (Researcher Int5)

From a scientific standpoint, there is value in placing relatively few restrictions on researchers’ use of genetic samples. Having been collected under broader consent, such samples have higher value to scientists because they may conduct more studies with fewer restrictions, publish more papers, and collaborate with more researchers. They are far more flexible for use by different researchers and in various technological applications.

At the same time, this consent makes samples the property of the research institution, leaving participants with little control over research uses. This transfer of control from the

participant to the IRB signals that, once donated, DNA samples belong to institutions; it is the responsibility of the institutions' infrastructure, such as an IRB, to ensure that they are used properly.

> There's a strong feeling, I think, among investigators that once we have the samples, the samples belong to the investigator and not to the subject any-more. (IRB chair Int6)

Because researchers and institutions assume ownership of the samples, many researchers have used them without much thought about how the donors of the samples might react. However, the Havasupai case challenged these notions of ownership, introducing a power struggle over appropriate use and stewardship of the samples. Furthermore, different actors and communities involved in research define value differently: value for researchers includes long-term viable samples while value to the donors (including the Havasupai tribe) includes some determination over their DNA samples and the intrinsic value of the DNA itself. The lawsuit suggests that participants maintained some expectations of ownership over their own biomaterials. The return of the samples was valuable to both the individual donors and the community. Value, then, like justice is neither uniform nor self-evident but takes on different meanings.

The "Co-evolution" of Informed Consent

Informed consent meanings and practices have been shaped through and by social processes. According to many of the interviewees, informed consent practices have "co-evolved" alongside advances in genetic research, and this evolution has cushioned researchers against the direct impact of the Havasupai case. As scientific knowledge advances, so do new consent forms to address new social and ethical issues; the two forms of knowledge are coproduced to address intersection of science, technology, and cultures of both scientists and research participants (Jasanoff 2004). The "evolution of consent" theme alongside the notion of time and advances in genetics pervaded the other major themes that emerged in these interviews: both researchers and IRB chairpersons stressed that consent practices have changed over time to cover new concerns, shape scientific practice and the way that scientists think about interacting with research participants, and what researchers deem allowable uses of samples. However, respondents were hesitant to suggest whether this evolution was progress or not, rather they emphasized that change has occurred over time and they have adapted. Regardless, the evolved informed consent forms generally did not solicit participant input, but instead required participants to waive their rights to their samples; in response, calls for creative solutions to allow participants more control and input would presumably increase trust and research participation (Winickoff and Winickoff 2003). Because of this co-evolution, some respondents did not perceive a direct impact of the Havasupai case on their own research. As one researcher described:

> And certainly, I think the Havasupai case really hasn't had an effect that I can see as much, mostly because the field was evolving along with it. It seems like it's just kind of co-evolution. (Researcher Int9)

The co-evolution of addressing informed consent issues in a climate of genetic advancement has created an environment in which some researchers perceive that research ethics issues

have been adequately addressed and will not affect current research. The Havasupai case is an old, outdated case in which some perceive no effect because the ethical issues that were raised have been addressed for new genetic research.

The advancement of both genetics and informed consent standards affects both IRBs and researchers; while researchers are pushed to imagine potential ethical issues, IRBs are simultaneously prompted to address technological advances in genetics. However, while IRBs do rely on researchers to lay out potential issues of the advancing technology, some researchers prefer to take a "backseat" approach in addressing research ethics and expect their IRBs to take responsibility for addressing the new ethical issues while they focus on their research. For example, one researcher learned to live with the new rules and abide by new ethical guidelines:

> I just feel like it's a learning process, and I feel like I'm continuously learning myself and adapting and we have to adapt to changes that occur either with the local populations or with the government that we work with. And as people are doing research on ethical legal issues in this field, we just have to continue to adapt. (Researcher Int13)

This backseat approach to dealing with change in genetic research studies allows others to take on the responsibility and carry out research on ethical and legal issues, come up with guidelines, and the researcher will adapt to those new rules and guidelines. Ethical issues can be learned and followed but some researchers choose not to worry about research ethics, forcing the IRB to take a more active role in ensuring that research ethics guidelines are followed and enforced.

Advances in the field of genetics have required investigators to shift their attention toward addressing the associated ethical and consent issues around informed consent, prompting gradual changes in informed consent procedures to ensure respectful relationships with research participants and ultimately avoid conflicts and lawsuits. Some new issues have emerged over control of samples: who owns the materials, who can make decisions about future uses, and what are acceptable uses of samples, all of which are commonly addressed in informed consent forms today. Additionally, as whole genome sequencing technologies have advanced, IRB chairs have been creating informed consent templates to ensure research participants fully understand the study and to address issues of privacy and implications for family members. However, broad consent forms might prove to be too vague for many potential research participants to understand, as was demonstrated in the Havasupai case, and may not allow for fair and equitable research opportunities for indigenous participants.

Genetics and ethical issues such as informed consent evolve slowly over time. When conflicts such as the Havasupai case arise, researchers and IRBs learn about the issues, but do not tend to make any immediate or drastic changes. Rather, IRBs note the events that catch their attention, and then they make small changes in incremental steps that add up to a larger, overall change over time.

> I think it would be somewhat naïve to say, 10 years ago was one way and today it's a different way. I mean much like every change that occurs, it gradually occurs. It evolves over time. There's nothing dramatic really about it. It's things that highlight

> or brings things to our attention. But it's basically a slow evolving process. (IRB chair Int18)

Although the Havasupai case came to this respondent's attention, any resulting change was perceived as gradual; one cannot pinpoint a specific event as the cause for change in informed consent.

Informed Consent as Safeguard

Most researchers and IRB chairs in this study preferred broad consent forms over specific or tiered consent forms to allow for the most flexibility with future uses of samples. While broad consent language can allow participants a chance to realize the broad spectrum of potential uses of their sample in research, these broad consent forms may actually provide a "cover" for researchers to do a wide range of research rather than addressing specific concerns. At the same time, broad consent both provides researchers with more leeway to conduct research and a way to safeguard researchers and IRBs against running into issues over restricted uses of samples. The safeguards that one puts in place could take the form of creating very broad consent language for researchers. A researcher considered broad uses in developing consent documents:

> When we design a consent, we try to think of all the possibilities, but you never really know because technology changes and all what we know about disease changes. (Researcher Int8)

Considering all the possibilities for current and future uses of samples is important for researchers and has been encouraged by IRB chairs. This particular IRB chairperson advocated the use of broad consents to allow for flexibility and possible future uses of samples using technologies that have not yet been developed.

> We encourage people to describe the types of research that may use the sample in the future, if applicable. Such as the fact that the cell lines may be immortalized, that there might be whole genome sequencing and that there might be injection of human cells into animals. So we try to pick out the facets that we think might be of concern to a very large population and put that in the consent form so that people are informed of that. So rather than being advocates of tiered consent, … we'd rather say, "Listen, you're giving broad permission for use of this, and that broad permission might include some of these kinds of things and if you don't want your cells used that way, then don't participate in the research." (IRB chair Int22)

However, broad language does not work for all; it fails to acknowledge that certain populations may not feel comfortable with certain types of research. The same respondent continues with,

> We may never run into any Havasupai Indian folks in our studies. So, rather than putting in specific concerns, we thought let's try to identify the ones that are of perhaps more widespread concern. (IRB chair Int22)

Rather than addressing unique community concerns, this IRB chair has shifted toward using broader informed consent forms in research. In this construction, the only choice involved in agreeing to participate in research is whether to participate or not; if one chooses to

participate, one must opt in to all potential uses. The only alternative posed here is to not participate, leaving little room for negotiation between researchers and research participants.

Researchers and IRBs rely on their informed consent language for security, guidance, and self-protection. The safeguards in place prevent some researchers from doing research outside of their original consent. In discussing the Havasupai case, one researcher said,

> Well, I think it'll just put more closer scrutiny, but I believe that we already have the safeguards in place that we are not allowed to do unfocused investigation research outside of the original project without separate consent, and again we have always had that in our consent forms and we don't do that kind of work. (Researcher Int11)

By refusing to expand the research focus beyond the scope of the informed consent documentation, this researcher expresses an attitude that relies on informed consent forms and IRB approval for protection and oversight and believes these documents act as a safeguard. The researcher does not want to violate the informed consent agreements, and thus puts the responsibility in the hands of the IRB. In this view, the IRB protects researchers through its guidance and through the informed consent documents it provides.

One IRB chairperson emphasized the importance of having an informed consent that clearly specifies the intended research goals of the researcher. One should not simply de-identify samples by removing personal identifiers, such as names and addresses, to be able to share them freely or use them for other studies beyond what they were originally consented for.

> You can't escape by hiding behind the de-identification model necessarily because it kind of identifies you already with [a] certain ethnic group or having a certain genetic disease carrier whatever it might be, it kind of has implications for the community that you are studying, whether you intend it to or not. (IRB chair Int3)

De-identifying samples in order to use them for studies beyond the informed consent is not a solution; the research may have implications for the community that identifies with that population, particularly in cases where population-based information may reveal potentially stigmatizing information for other individuals of the same population or ethnic group.

Discussion and Conclusion

Scientific knowledge production in genetic research relies on collecting DNA samples from participants, followed by the ability to study those samples to identify genetic variants of interest. The findings are then published, often having some effect on both the participant community and the scientific community. As scientists build on published knowledge and advance their careers and discipline, communities seldom receive any tangible benefits from research participation. While researchers do think of implications for human health, they do not necessarily discuss the broader societal responses to their research process (Jasanoff 2005).

As evidenced in interviews with IRB chairs and researchers in this study, there is a range of views within the research community on the Havasupai case and whether it had an impact on

informed consent in human genetic research studies. It is important to note that there was no court ruling and the case was dismissed due to a procedural error, resulting in no legal precedent from the Havasupai case and leaving ambiguity over how the informed consent forms should have been interpreted. However, the case settled in the tribe's favor and the Arizona Board of Regents agreed to provide monetary and other forms of assistance to the Havasupai, thus suggesting that the Havasupai had a convincing argument about not having truly informed consent, therefore raising the bar for improving ethical standards in research.

While many respondents said they were not affected by the case, many reported that the case made them more aware of the complexity of informed consent, including concerns of indigenous peoples and cultural issues related to the Havasupai Tribe. When pressed further, many respondents espoused a belief that informed consent practices have been evolving over time and that today's standards are adequate and would protect them from entering into troublesome situations. Further, many respondents felt that there were safeguards in place, primarily in the form of informed consent documents that protected them from encountering issues and conflicts with their research participants. However, confusion has arisen over the appropriate uses of previously collected biological materials, in particular DNA samples, that have become very valuable and the question of appropriate uses posed challenges for researchers who want to use them for new studies.

Some respondents viewed DNA samples as a valuable resource, especially those originating from isolated populations. Others described some of the challenges in working with communities to collect these valuable resources. The widespread concerns over what to do with old DNA samples pose challenges in dealing with old informed consent, particularly in working with contemporary populations. As samples became more valuable over time, they became practically unusable because the informed consent that was given, if any, would not allow for modern day use of the samples. For some, the Havasupai case raised awareness of appropriate uses of old, valuable DNA samples.

New issues in genetics such as advancing technologies, appropriate uses of samples and ensuring appropriate informed consent have become interwoven as ideas about science and their pertinent ethical issues co-evolve and shape each other as new knowledge is produced (Reardon 2005). Reflections of researchers and IRB chairs reveal how scientific culture and practices influence interactions among IRBs, researchers, and participants; IRBs review protocols, researchers carry out studies, and participants contribute their samples for scientific discoveries. When participants are dissatisfied, they may voice concerns to the researcher who then reports to the IRB. Decisions to amend research protocols or informed consent forms ultimately rest with the IRB, which retains authority over research and all proposed changes. Thus, changes to informed consent documents may co-evolve during a research study or over a much longer period of time based on multiple influences.

The Havasupai case did not directly cause broad change, but repercussions of incomplete informed consent have resonated within the research community. Additionally, other issues with informed consent and secondary uses of samples have come to light over the last twenty years: concerns were raised about the syphilis studies on African American males in Tuskegee, uses of newborn screening samples in research without informed consent from

parents, and cancer cells removed from Henrietta Lacks that were then cultured and used in research without her knowledge (Reverby 2009; Ramshaw 2010; Skloot 2010). In response, policy makers, bioethicists, and IRBs have been suggesting more stringent review processes, more detailed consent forms, and additional human subjects' protections including increased communication and disclosure to research participants. Researchers adopt or adapt these new rules and guidelines to their research so that this shift in thinking about informed consent has occurred gradually, and is therefore nonobvious, thus making it difficult to pinpoint just how the Havasupai case had an impact on research as compared with the independent evolution of informed consent.

Interestingly, in this study, IRBs and researchers have shifted toward using broad consent language to safeguard themselves by avoiding potential issues and increased restrictions with future uses of the samples. However, broad informed consent forms may actually hinder research participation from minority or indigenous people, and the only alternative these consent forms provide seems to be nonparticipation. Small, isolated populations like the Havasupai and the unique cultural challenges posed by the group are not considered when broad consent forms are being created. Rather, the issues that are considered are generally more broadly relevant to other populations and research participants, furthering the divide between those populations who decide to participate and are thus more likely to benefit and those who are not (Epstein 2007). There is less incentive to tailor research protocols to take in to account the concerns of small populations in genetic research except in cases where researchers take the initiative to engage the community in discussions about the research and modify informed consent templates to address specific concerns of the community; failing to do so, however, further marginalizes these groups and makes them less likely to participate in research (Goering, Holland, and Fryer-Edwards 2008), therefore excluding certain minority groups from participating in research. Exclusion of these groups may be an unintended consequence of IRBs creating broad consent language resulting from new regulations, but do not address ethical concerns or justice issues of having equal access to research participation.

This case reveals the necessity of thinking deeply about the role of regulation and justice issues in genomics research, especially as new technologies and informed consent procedures are developed. Recognizing the issues in informed consent and participant desires to maintain some control, new proposed models for informed consent in biobanking would give more power to participants by allowing them to opt in or opt out of certain types of research (Saha and Hurlbut 2011). Increased regulation and broad consent language may confine the IRB to focusing on and addressing issues related to risk, benefit, and proper informed consent and shift attention away from thinking about equal access and potential benefits to communities from research participation. We must remain mindful of the diverse views of research participants and work harder to ensure that just and equitable research practices encourage communication and inclusion of minorities in research in order to breakdown the barriers of distrust.

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Biography

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