Published in final edited form as:
AJOB Prim Res. 2013 October 1; 4(4): 55–63. doi:10.1080/21507716.2013.770104.

Awareness and Acceptable Practices: IRB and Researcher Reflections on the Havasupai Lawsuit

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Abstract

Background—In 2003, Havasupai tribe members in Arizona discovered that their DNA samples, collected for genetic studies on Type II diabetes, had been used for studies on schizophrenia, migration, and inbreeding without their approval. The resulting lawsuit brought by the Havasupai reached a settlement in April 2010 in which tribe members received monetary compensation and the return of DNA samples. In this study, we examine the perceptions of Institutional Review Board (IRB) chairpersons and human genetic researchers about the case and its impact on the practice of research.

Methods—Twenty-minute semi-structured interviews were conducted with 26 Institutional Review Board (IRB) chairs and researchers at six top NIH-funded institutions. Participants were questioned about their knowledge and perceived impact of the Havasupai case and their perceptions of informed consent in genetic research studies.

Results—We found that most study participants did not perceive that the Havasupai case had a large impact. However, we identified key concerns and opinions of the case, in particular, increased awareness of culturally sensitive issues with informed consent and secondary uses of samples.

Conclusions—The results provide a deeper understanding of how informed consent issues are understood by IRB members and human genetic researchers and the implications for research ethics education.

Keywords

Research Ethics; Informed Consent; Institutional Review Boards; Havasupai

INTRODUCTION

In 2003, members of the Havasupai tribe in Arizona discovered that their DNA samples, collected between 1990-1994 for genetic studies on Type II diabetes by researchers at Arizona State University, had also been used without their knowledge or explicit approval for studies on schizophrenia, migration, and inbreeding. The Havasupai Tribe, a sovereign entity with its own government, filed a lawsuit in 2004 over lack of informed consent and misuse of genetic materials, which signified an important moment in which research subjects took a stand and initiated legal action against researchers over misuse of DNA

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samples (Havasupai Tribe of the Havasupai Reservation v. Arizona Board of Regents and Therese Ann Markow 2004).

The written informed consent documents that were used during recruitment stated, “the purpose of the research is to study the causes of behavioral/medical disorders” (Hart 2003, 1). Further evidence suggested that members of the research team failed to disclose intentions to study schizophrenia to the Havasupai; they were told by the principal investigator to search medical records for evidence of schizophrenia, but did not have explicit approval from the tribe (Hart 2003). The case eventually reached a settlement in April 2010 in which tribe members received monetary compensation of $700,000, funds for a clinic and school, and the return of DNA samples (Harmon 2010).

The Havasupai case generated many discussions both within the genetics world and in indigenous communities about its implications for tribes who are already distrustful of research and for researchers who diligently adhere to ethical guidelines while working with indigenous communities. Significant media attention was paid to the case; it appeared on the front page of *The New York Times* (Harmon 2010), and was featured in *Nature Magazine* (Dalton 2004), *Phoenix Magazine* (Bommersbach 2008), and the *New England Journal of Medicine* (Mello and Wolf 2010). Moreover, Dr. Roderick McInnes brought attention to the issues raised in the Havasupai case to human genetic researchers during his Presidential Address at the 2010 annual American Society of Human Genetics (ASHG) meeting, marking a significant moment in which indigenous issues in research ethics were placed in the forefront of attention for human geneticists. The speech was subsequently published (McInnes 2011), extending its impact and audience. Furthermore, the Havasupai case has been discussed at conferences and in webinars targeted at researchers, Institutional Review Board (IRB) members, and human research protection programs (Public Responsibility in Medicine and Research 2010). The extensive publicity about the case garnered attention in research circles, presenting opportunities for researchers and IRB chairs to learn about the case and the issues that were raised regarding informed consent and secondary uses of samples.

Despite the widespread attention the case received, many questions surrounding the case remain unanswered, and there is little guidance for how to deal with these types of cases in the future. The resolution of the Havasupai case was an out-of-court settlement, therefore no legal precedent was created to which IRBs and researchers could turn to for guidance on informed consent or secondary uses of samples. Thus, the broader impact of the Havasupai case on biomedical research remains largely unknown.

We conducted interviews with IRB chairs and genetic researchers to determine their perceived responsibilities to research participants, and acceptable uses of biological materials, primarily for secondary uses. Some studies have looked at how researchers view their responsibilities to their research participants by acknowledging and recognizing the implications of their work (Ladd et al. 2009; McCormick, Boyce, and Cho 2009). Other studies have shown that research participants value being asked for permission for secondary uses of their samples, especially if they were to be stored in a federal repository (Ludman et al. 2010; Trinidad et al. 2011). Furthermore, other studies have shown that research participants of diverse ethnic backgrounds have different opinions on informed consent that influence their expectations of the research process; participants are influenced by their cultural backgrounds and communities and by the perceived risks, burdens, and benefits of participation (Lakes et al. 2012).

Some studies have reported mixed consensus of IRB and researcher opinions on re-consent for secondary uses of samples (Edwards et al. 2011) or on the burdens that IRBs place on

researchers, which do not always result in increased human subjects protections and may actually hinder genetic research (Silberman and Kahn 2011), further demonstrating a need for increased discussion of ethical issues that arise in the context of appropriate uses of genetic material in research. The proposed changes to the Common Rule contained in the Advanced Notice of Proposed Rule Making encourage a broader consent to maximize the usefulness of samples (Department of Health and Human Services 2011); however, this broad consent for wider use of samples may be in conflict with the concerns raised by the Havasupai tribe.

The purpose of this study is to explore the extent to which the Havasupai case has affected the current human genetic research environment, in particular how knowledge of the case has affected conversations about informed consent and appropriate uses of human biological materials. Through semi-structured interviews with IRB chairs and researchers, we have identified a range of perceptions of the case and opinions about informed consent from IRB chairpersons and biomedical researchers engaged in genetics research involving human subjects. The results provide a deeper understanding of how concerns raised by the lawsuit affect decisions made by human research review boards and researchers in the context of genetic research. In particular, discussions about the impact of the case have revealed new awareness of informed consent issues, the importance of recognizing and addressing cultural differences, and acceptable uses of biological materials that stem from informed consent agreements.

METHODS

Participant Recruitment

The study population consists of IRB chairpersons and biomedical faculty researchers at six National Institutes of Health (NIH)-funded medical schools across the US that were identified from the top 10% of the ranking tables for 2009 based on data from the NIH (Blue Ridge Institute for Medical Research 2009). These institutions were chosen with the assumption that higher levels of NIH funding at medical schools correlates with a larger number of biomedical research projects and thus the potential for biomedical researchers doing human subjects and genetic research. Three of the institutions were on the east coast, one was in the mid-west, and two were on the west coast of the U.S.

Participants were targeted for recruitment if they were (1) IRB chairs listed on an IRB roster at the institutions included in this study or (2) researchers identified through search results of the included institution's website using the following search terms: "human," "genetic," "sample," "DNA," and "population." Potential participants were invited to the study through a recruitment email letter asking them to share general perspectives on informed consent practices, the use of human genetic samples in research studies, and the impact of the recent lawsuit involving the Havasupai Tribe and Arizona State University. Participants were asked to provide verbal consent to a 20-minute audio-recorded interview. The study was approved by the IRB at Stanford University.

Data Collection and Analysis

Interviews lasted approximately 20 minutes and were conducted using a semi-structured interview guide that included questions about an IRB chairperson's current involvement in protocol review (Table 1) or a researcher's involvement in human genetic research (Table 2); their understanding of and perceptions of the Havasupai case; and their opinions on informed consent. Interviews began with the following script:

> "As a brief introduction to this interview, I am interested in the impact of the recent Havasupai lawsuit on genetic research studies that was settled in April of this year.

> This will hopefully provide a deeper understanding of how conflicts in genetic research affect [IRB chairs and researchers]."

Interviews were conducted in a confidential manner and identifiers were removed to maintain the privacy and confidentiality of each participant. All participants consented to audio-recording and transcription of the interviews, and each participant was offered a $25 gift certificate in exchange for participation. All interviews were recorded, and audio files were transcribed and independently reviewed for accuracy.

Knowledge about the case was measured by identifying the facts that were cited by the interviewees when they were asked to describe what they knew about the case. These facts included mentioning the intended research focus area (studies on diabetes); secondary uses of samples (studies on schizophrenia and studies involving human migration or origins); the ethical issue(s) that arose (e.g., that the Havasupai claimed lack of informed consent or did not agree to give permission for studies beyond diabetes); and a description of the settlement terms (financial compensation and the return of DNA samples to the Havasupai Tribe).

RESULTS

Participants

A total of 122 individuals (38 IRB chairs and 84 researchers) were contacted and invited to participate in an interview. Of these, 18 declined participation and 78 did not respond to the email invitations, despite multiple attempts. Those who declined gave reasons such as being too busy, not being involved in the informed consent process, not knowing enough about the topic, or thinking that the study does not apply to them.

Interviews were then conducted with 13 IRB chairs and 13 human genetics researchers (21.3% overall response rate) from departments including Genetics, Medicine, Biochemistry, Biology, and Nursing. The academic positions of IRB chairs ranged from associate professor to emeritus professor whereas the academic positions of researchers ranged from assistant professor to full professor. The study sample was comprised of 17 men (8 IRB chairs and 9 researchers) and 9 women (5 IRB chairs and 4 researchers) and the numbers were approximately distributed across all six institutions. There were 2-7 respondents from each institution with at least one researcher and one IRB chair at each institution. Interviews took place in person or by telephone between November 2010 and September 2011. Recruitment ceased when we reached theoretical saturation and no new themes emerged in the data.

Several respondents in this study had previous experiences working with minority populations. Two respondents reported having ties to the Havasupai sample; either they had used data derived from Havasupai samples or knew someone personally who had and were contacted with requests to return samples. Three other respondents worked with other tribes in the US and felt that they were more sensitive to cultural differences, which gave them a deeper appreciation of the issues raised by the Havasupai case. Three other respondents worked with minority and/or vulnerable populations (that were not Native American) both within the US and internationally.

Transcripts of all 26 interviews were imported into NVivo 9 software for qualitative data analysis. The data were iteratively coded, and recurring themes were identified from the data. A second researcher trained in qualitative research methods independently coded a 15% sample of the interviews. Disagreements that were identified were resolved, achieving a Cohen's Kappa statistic of 0.81 measured by SPSS software v.20. Data on the statements relevant to perceptions and impact of the Havasupai case are reported here.

Knowledge of the Havasupai case

Participants in this study were asked to describe their knowledge about the events and ethical issues raised by the Havasupai case. Most IRB chairs (12 out of 13) named an ethical concern in describing the Havasupai case whereas only half of the researchers (7 out of 13) were able to describe an ethical issue. Overall, IRB chairs knew more facts about the case than researchers. On the other hand, three researchers did not know about the case or could not remember details and did not cite any facts about the case; of these, two researchers said they had not heard of the Havasupai case but, because the interview included questions on informed consent and human subjects participation, these individuals still agreed to be interviewed.

The respondents described ethical issues such as how the Havasupai disagreed with the secondary uses of the samples that were outside of the original intent of the proposed research, and that the secondary uses of samples (such as on migration studies) went against Havasupai beliefs about their own origins. One IRB chair described the case and the ethical issues as follows:

> "So, it was a research study being undertaken at Arizona State University. They obtained samples from this particular tribe. They consented them to analyze the samples for one particular area. However, the investigators did additional analysis on the samples. If I remember correctly it was to study different components of mental disease and the associations of mental disease to the origins of the tribe itself. So, the case [inaudible] was that the participants didn't consent to the genetic testing being done for that specific association, so that the concept was that it wasn't complete consent." (IRB Chairperson Int18)

This IRB chair described how the Havasupai participants did not give "complete" consent to studies on mental disease and beliefs about tribal origins based on migration studies.

A researcher described other ethical issues about the case:

> "I guess what I know is that the Havasupai sued the university or the researchers because they didn't like the way their blood samples were used for genetic research. They had, I think, initially consented to a study of diabetes and felt that some other research that was done on their genetic history and maybe on the mental illness or schizophrenia was outside of what they had agreed to." (Researcher Int8)

This researcher noted that the Havasupai participants had given consent for studies on diabetes, but did not agree to the studies on migration studies ("genetic history") or schizophrenia.

Overall, IRB chairs mentioned the ethical issues around informed consent and the Havasupai Tribe's objection to genetic studies on migration or origins more frequently than researchers did. Although some interviewees mentioned secondary uses for psychiatric disease, it was not mentioned as frequently as the studies performed on migration and human origins.

Perceived impact of the Havasupai case on human genetics research

Upon describing the case, participants in this study revealed a range of reactions to the Havasupai case and how it affected their research. Most IRB chairs and researchers in this study said their protocol review practices or their research agendas were not affected by the Havasupai case. Reasons for not being affected by the Havasupai case ranged from not being in a relevant research setting (such as working with tissue banks instead of collecting new samples, or not conducting the informed consent process) to statements that they had already taken action to prevent misunderstandings with their research participants (such as

having safeguards in place, having specific language in informed consent documents, and adhering strictly to the informed consent agreement).

For example, when asked about whether or not the Havasupai case had an effect on his work, one researcher responded:

> "Not in any direct way simply because, uh…, we would be really interested in working with Native communities in the U.S., but we're just not." (Researcher Int4)

This researcher did not see the issues of the Havasupai case as extending beyond the boundaries of his specific research foci or populations because his study populations were not Native American. As revealed later in the interview, this researcher had in fact worked with indigenous groups outside of the U.S., but did not have access to tribes in the U.S.:

> "We worked with investigators that were already on the ground working with groups that could help both enroll individuals and tell them about this project." (Researcher Int4)

Rather than working with Native American communities directly, this researcher had focused instead on collaborations with researchers who did have connections with different community groups.

Many IRB chairpersons in this study felt that while the Havasupai case raised issues in genetic research, they had not made dramatic changes to their review processes as a result. The Havasupai case received some attention and prompted discussion among some IRB members at their institution's IRB meetings or at national conferences, but it did not appear to change their overall perceptions of how informed consent should be conducted. However, IRB chairs thought that discussions about the Havasupai case and other similar cases have contributed to broader changes in thinking about informed consent. As described by one IRB chairperson:

> "Being in genetics and going to seminars weekly for years, I've known about these kinds of concerns for a long time. This [Havasupai case] event got a lot of publicity. So, I don't think that I changed my ideas because of this event." (IRB chairperson Int21)

Although the Havasupai case in particular may not have been perceived to have a huge effect on human genetic research, the combined effect of other cases appears to have a larger overall effect on informed consent.

The Havasupai case was one of many cases that contributed to the slowly changing view on informed consent issues. Issues in informed consent have been highlighted and debated in the context of other cases. In describing an increased awareness of informed consent issues and gaining a deeper understanding of the reasons for non-participation and mistrust in certain communities, several respondents in this study spontaneously cited examples such as the Human Genome Diversity Project (HGDP), the Tuskegee study on syphilis in African American men, and the case of cancer cells taken from Henrietta Lacks.

For example, one researcher described how the HGDP influenced his thinking about informed consent:

> "We were asked to evaluate the Human Genome Diversity Project at the time and so I was on that committee and we took lots of testimony … from many different groups including American Indian groups and other groups, as well as researchers in the area. And that's where I really got educated about informed consent, when it deals not so much with individuals." (Researcher Int17)

This researcher felt that issues in informed consent were raised for individuals and for groups.

Another researcher described the difficulties in working with African American communities, in part due to a long history of mistrust.

> "If you ever work in a study where you try to recruit African Americans you will know it. It is always so hard to get them to consent to research. And historically this has to do with a lot of African American abuses, you know the Tuskegee Airmen [sic] study and they were used without consent for scientific research in sort of very objectionable ways. And this is still recent enough in their memories; the 40s, the 50s, the 60s of the last century. That there still is a general distrust of researchers among African Americans." (Researcher Int26)

The researcher recognized the tension in African American communities that make it difficult to recruit them into research studies.

Another researcher described an increased awareness of issues in informed consent and trust that came from the recent book *The Immortal Life of Henrietta Lacks*:

> "It's an issue that I was aware of outside of the case and I recently read the book about Henrietta Lacks, and so forth, so I did, I think, pass along an article about the Havasupai case to my study coordinator to make sure she's aware of these issues, but I can't say that that case in particular changed my thinking a lot." (Researcher Int8)

This researcher maintains that the Havasupai case did not have much of an effect. However, this researcher did send along an article about the Havasupai case to ensure awareness within their research group.

Two respondents in this study described other researchers they knew of who were more directly affected by the case because they had used Havasupai samples and were forced to return them when the case settled. As an IRB chair stated:

> "We certainly talked about the case at IRB meetings and there's some investigators here who are population geneticists and used samples from this tribal group and from many tribal groups all across the world who were quite affected by it." (IRB chairperson Int21)

This IRB chair mentioned that the investigators who used Havasupai samples in their own research were affected by the case, and went on to elaborate:

> Interviewer: How did the case affect some of those individuals who had used the samples?
>
> IRB chair Int21: They had to give them back.
>
> Interviewer: And was that difficult to do?
>
> IRB chair Int21: I don't think it was physically or financially all that difficult. It challenged some of their research and there were misgivings about 'is this legitimate?' to undermine some of the findings or some of the things that we wanted to report. And they lived with that and they did it.

For the researchers who actually obtained and used Havasupai DNA samples, the samples had to be retrieved from their freezers and returned to the tribe. However, most of the interviewees in this study believed that they were not directly affected by the case.

Increased Awareness of Cultural Issues

Despite an overall lack of perceived impact, both IRB chairs and researchers in this study noted that the Havasupai case raised awareness of culturally sensitive issues, particularly in the context of secondary uses of samples. In general, IRB chairs were more concerned with dealing with culturally sensitive issues through research regulation and acting on their policies. One IRB chair described the impact of the case on cultural sensitivity:

> "I think it's just a little bit of a wake-up call that yes, you give 'lip service' to cultural sensitivity. We need to make sure that we are dealing with it as a real issue, and not just writing it in a little policy paragraph and filing it away somewhere." (IRB chairperson Int3)

Previously, potential problems were avoided through the provision of guidelines or recommendations, but with little enforcement or follow up. The Havasupai case demonstrated to the IRB chairperson that cultural sensitivity to issues in genetic research had not been taken seriously enough; creating policy without enforcement was no longer acceptable.

Researchers also saw the Havasupai case as a "wake-up call" for those in their field to learn about cultural issues; the limits of informed consent, such as ensuring participants understand how their samples will be used and obtaining truly informed consent; and their responsibilities toward research participants. The Havasupai case raised their awareness about how misunderstandings between researchers and participants can arise over different interpretations of informed consent. For example, one researcher described how the Havasupai case raised awareness and exposed the researcher to multiple sides of the issue:

> "I think it's made us aware of a lot of the sensitivities and the potential for misunderstanding. As an investigator, you see it from multiple sides." (Researcher Int4)

For this researcher, it is complicated and difficult to strike a balance between carrying out research and ensuring the participants are satisfied; this researcher was sympathetic to the researchers involved in the Havasupai case, but, on the other hand, was also sensitive to the issues around informed consent raised by the Havasupai Tribe.

The Havasupai case raised awareness for IRB chairs and researchers in different ways about appropriate uses of samples, proper informed consent, and potentially sensitive research. IRB chairpersons tended to think about the implications of potentially damaging research and took on the responsibility to do so, but some IRB chairs also thought that researchers were unaware of the issues or the Havasupai case:

> "I think it made us think more clearly about the implications. … I think the researchers are much less aware of it." (IRB chairperson Int19)

However, some researchers thought the case did indeed raise awareness of researchers' obligations to understand and become aware of the issues over informed consent. One researcher described that obligation and its potential consequences:

> "Yeah, it's an obligation to understand [the issues], 'cause you screw things up badly, and you will do it unintentionally, but it still makes you responsible 'cause you didn't figure it out." (Researcher Int1)

This researcher felt there was a responsibility for human genetic researchers to understand the issues within a community. Other researchers in this study felt that it was their responsibility to become aware of the issues in order to address potential problems early and to avoid negative consequences and conflicts with one's research participants:

> "I do think it's raised awareness of human subjects research and concerns. You want to be as careful as you can, and that any potential concerns you try to nip in the bud and address as early as you can. No matter who's right or who's wrong, you should not end up in court with your research subjects, right? That's a really bad outcome." (Researcher Int4)

In addition to highlighting the negative consequences of legal action, by not addressing concerns early, researchers run the risk of severing researcher-participant relationships. As this researcher noted, one should be careful to address concerns early.

Acceptable uses of samples

When asked about their opinions of informed consent, most interviewees in this study spontaneously discussed acceptable research uses of biological materials and the rules governing those uses. Questions about the Havasupai case and informed consent spurred discussions about appropriate uses of samples, both in the Havasupai case and at the interviewees' own institutions. Both IRB chairs and researchers discussed the importance of having informed consent that allows research participants to fully understand how their samples will be used. While there was a debate over how much information should be given to participants, interviewees agreed that it is always important to obtain informed consent. However, one IRB chair shared concerns about how broad informed consent raises the issue that consent form language has become vague or generic, making it difficult for participants to fully understand how their samples will be used:

> "People don't know what they're consenting for when you're so generic about what might happen with their sample and that we aren't going to allow people to do [broad consent]. And, others argue that many people don't care." (IRB chairperson Int25)

This IRB chair notes the tension between consenting so broadly that a participant would not understand, while other participants might not care about how their samples are used.

A researcher echoed a similar sentiment; research participants might not be bothered by giving broad consent for how their samples will be used and would instead want it to be used for multiple studies. This researcher elaborated:

> "Honestly in talking to people who participate in my research, most of them, you know, they're giving the sample and they really want it to be as useful as possible. I think it's probably the exception rather than the rule that people really want their sample to be highly restricted." (Researcher Int8)

This researcher advocated for broad informed consent to allow samples to be useful for multiple purposes. Yet, not all respondents in this study agreed with that assessment.

Others discussed the importance of outlining specific uses of samples. Many researchers and IRB chairs agreed that disclosure of how and for what purposes the samples will be used was important, and that researchers should abide by the agreement made with the research participant. One IRB chairperson described the importance of disclosure of study goals to research participants:

> "For me, the bottom line is that the researchers need to disclose to the study participants in this kind of a study where they might be using research specimens at a future time for things that were different from the original study than through which the samples were gathered, that they be as specific as possible in describing all of the types of different things that might happen with those specimens." (IRB chairperson Int3)

This IRB chair thought that it was important to disclose all future intended research uses of samples.

Along the same lines, one researcher emphasized the importance of staying within the boundaries of the original informed consent agreement.

> "You understand the temptation to say, 'Okay I've got these samples. I can use them for a lot of different things. They've been consented for genotyping or whatever, I'm just gonna go ahead and use them.' Uh, versus the reality that if you've said your going to use them for A and you want to use them for B, and B is really different than A, then you can't do that without getting not only new [consent], it also depends." (Researcher Int4)

The informed consent form provides boundaries for determining acceptable and unacceptable uses of samples. This researcher describes the temptation to push the boundaries to use the samples for other studies while also acknowledging what studies are acceptable or not according to the original consent. For this researcher, obtaining new consent from the research participants may allow one the permission necessary to carry out new studies.

While there was no consensus over whether researchers should obtain consent for broad uses or specific uses of samples, obtaining informed consent was viewed as important. Once obtained, researchers and IRBs expressed a variety of opinions over how the samples could be used in research.

DISCUSSION

Overall, most IRB chairpersons and researchers in this study were able to articulate the ethical issues that arose from the case, but they report no direct or personal impact of the Havasupai case on their work because they thought that the issues that were raised did not translate over to their own work with human research participants. Despite the lack of perceived impact, respondents in this study did believe that the case raised awareness of cultural sensitivity and potential issues in genetics, implications of potentially stigmatizing research for communities, permissible uses of biological samples, and some felt that informed consent should be much more transparent. However, some researchers and IRB chairs in this study thought that once donated, research participants do not care how their samples are used in research. Researchers in these interviews thought it was their responsibility to become aware of the issues in human genetics research, whereas some IRB chairs thought that researchers were not as aware as they could be.

The Havasupai case is not unique, but instead joins a growing number of cases generating attention for misuses of samples in biological research. The participants thought that the issues raised in the Havasupai case did not result in dramatic changes to scientific practice because the case is part of a larger movement in thinking about informed consent. Other cases, policy changes, and discussions have contributed to overall awareness of issues in human genetics research for IRBs and researchers. For example, some interviewees cited other examples of this movement, such as *The Immortal Life of Henrietta Lacks*, which describes how cervical cancer cells were taken from a poor African American patient, grown in cell-culture into the *HeLa* cell line, and made available to scientists worldwide, without obtaining her consent to use the cells in research (Skloot 2010). Other examples mentioned in these interviews included the concerns about lack of full informed consent in the Public Health Service syphilis studies in males at Tuskegee who were denied treatment in the name of understanding the natural progression of the disease, even after treatment became

available (Reverby 2009). Respondents in this study also mentioned the hesitation and distrust of HGDP researchers by various population groups in the 1990s (Greely 2001).

Further, questions were raised about obtaining group consent from population groups in addition to obtaining individual consent from each research participant (Greely 1998; Harry 1995). Policy changes at the federal and institutional level have also led researchers and IRBs to comply with rules and recommendations through the Belmont Report that identified principles of autonomy, beneficence, and justice (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978) and the Code of Federal Regulations that requires IRB oversight of human subjects research (Department of Health and Human Services 2005). More recently, the proposed changes to the Common Rule have renewed attention to discussions on informed consent. Together, these examples have led IRBs and policy makers to make gradual changes to informed consent, and researchers have adapted to these rules and regulations.

It is troublesome that some researchers perceived that the general issues raised by the case did not apply to them, which is consistent with other studies showing that researchers believed their research did not have broader ethical or societal implications (McCormick, Boyce, and Cho 2009). It is also troublesome that some researchers perceive that research participants don't care how their samples are used, given that several studies have shown that research participants would actually like to know how their samples are being used, and be asked for permission for new uses, especially if they were to be used in secondary studies (Carmichael 2011; Ludman et al. 2010; Tarini et al. 2010). For example, 90% of participants in a recent survey who had previously given permission for one study felt it was important to be asked for permission to add their data to a databank to be accessible to other researchers; most of the participants who wanted to be asked for permission eventually agreed to contribute their samples, but noted that their initial permission did not automatically extend to secondary uses of their data (Ludman et al. 2010). In some communities, research participants may decide not to participate in research due to mistrust of research and the healthcare system (Scharff 2010; Brandon, Isaac, and LaVeist 2005; Harmon 2006). We encourage researchers to build trust into research partnerships, regardless of community participation or individual participation, through transparency of research progress and regular communication; by returning research results to the community; and by inviting community input when pursuing new directions, even if the new directions are thought to fall within the original informed consent agreement.

A major limitation of this study was our low response rate, which may have been biased towards individuals who were interested in the topic. Additionally, the participants were recruited from top NIH-funded research institutions, so their experiences and reflections may not be generalizable to all IRB chairs and researchers. Anecdotal evidence suggests there was a large impact resulting from the Havasupai case at universities in Arizona; thus, it would be interesting to study the larger impact of the case at those institutions. While we recognize that this limits the overall generalizability of the findings, we believe that our qualitative analysis reveals specific issues that indicate particular needs for researcher education.

Specifically, we call attention to a need to increase awareness of how this case applies to all researchers and institutions, not merely those involved in research on the Havasupai or with Native Americans. The Havasupai case highlighted the need to better understand what constitutes full informed consent, to consider implications of ones' research in order to avoid potentially stigmatizing results, and to address sensitive issues that arise when working with vulnerable populations. Informed consent language should be made more explicit to avoid ambiguities in interpretation, regardless of whether the forms are written

with broad or tiered consent options. The proposed changes to the Common Rule encourage broader informed consent to provide researchers greater flexibility to carry out genetic research studies; however, broad consent might not be an effective means for gaining community support for research, making it more likely for issues around informed consent to arise again (Department of Health and Human Services 2011).

Researchers and IRBs need to become savvier at addressing culturally sensitive issues upfront. In the Havasupai case, members of the research team noted potential issues throughout the diabetes study such as being told not to discuss schizophrenia with Havasupai members, and to go through hospital records to search for evidence of schizophrenia without explicit approval, but little effort was made to remedy them (Hart 2003). Furthermore, researchers and IRB members should be better educated about the literature on research participant preferences and attitudes towards the use of their samples and about culturally sensitive issues.

Our results suggest a need for increased awareness of research ethics to address concerns early. We encourage researchers to learn to recognize ethics “triggers” early in their research and to discuss the issues with their IRBs and ethicists (Havard, Cho, and Magnus 2012). Furthermore, recognition of the importance of research ethics consultations is growing, and models have been proposed for researchers and IRBs to work together to resolve ethics issues early (Cho et al. 2008), especially those for which explicit regulatory boundaries have not been set, such as regarding secondary use of biological samples. It appears that many researchers have not learned important lessons from the Havasupai case and that without successful research ethics education, history could repeat itself.

Acknowledgments

N.A.G. acknowledges support from NIH/NHGRI F32 HG005931. M.K.C. and N.A.G. acknowledge support from NIH/NHGRI P50 HG003389.

REFERENCES

Blue Ridge Institute for Medical Research. Blue Ridge Institute for Medical Research 2009. 2010. NIH Awards to Medical Schools by Rank Fiscal Year 2009. [cited August 27 2010]. Available from http://www.brimr.org/NIH_Awards/2009/NIH_Awards_2009.htm

Bommersbach, J. Arizona’s Broken Arrow 2008. Available from http://www.phoenixmag.com/lifestyle/200811/arizona-s-broken-arrow/

Brandon DT, Isaac LA, LaVeist TA. The legacy of Tuskegee and trust in medical care: is Tuskegee responsible for race differences in mistrust of medical care? Journal of the National Medical Association. 2005; 97(7):951–6. [PubMed: 16080664]

Carmichael M. Newborn screening: a spot of trouble. Nature. 2011; 475(7355):156–8. [PubMed: 21753828]

Cho MK, Tobin SL, Greely HT, McCormick J, Boyce A, Magnus D. Strangers at the benchside: research ethics consultation. American Journal of Bioethics. 2008; 8(3):4–13. [PubMed: 18570086]

Dalton R. When two tribes go to war. Nature. 2004; 430(6999):500–2. [PubMed: 15282577]

Department of Health and Human Services. Protection of human subjects. Title 45, Code of Federal Regulations, Part 46. Department of Health and Human Services: US Department of Health and Human Services, National Institutes of Health, Office for Protection from Research Risks. , editor. 2005.

Department of Health and Human Services. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators. In: Department of Health and Human Services: Federal Register. , editor. Federal Register. 2011.

Edwards KL, Lemke AA, Trinidad SB, Lewis SM, et al. Attitudes toward genetic research review: results from a survey of human genetics researchers. Public Health Genomics. 2011; 14(6):337–45. [PubMed: 21487211]

Greely HT. Legal, ethical, and social issues in human genome research. Annual Review of Anthropology. 1998; 27:473–502.

Greely HT. Informed consent and other ethical issues in human population genetics. Annual Review of Genetics. 2001; 35:785–800.

Harmon A. DNA Gatherers Hit Snag: Tribes Don't Trust Them. The New York Times. 2006

Harmon A. Indian Tribe Wins Fight to Limit Research of Its DNA. The New York Times. Apr 22.2010 2010

Harry, D. Indigenous Peoples' Council on Biocolonialism 1995 [cited November 26 2009]. 2009. The Human Genome Diversity Project and Its Implications For Indigenous Peoples. Available from http://www.ipcb.org/publications/briefing_papers/files/hgdp.html

Hart S, Sobraske K. Investigative Report Concerning the Medical Genetics Project at Havasupai. Arizona State University Law Library. 2003

Havard M, Cho MK, Magnus D. Triggers for research ethics consultation. Science Translational Medicine. 2012; 4(118):118cm1.

Havasupai Tribe of the Havasupai Reservation v. Arizona Board of Regents and Therese Ann Markow. 2004. Coconino County, Superior Court of Arizona.

Ladd JM, Lappe MD, McCormick JB, Boyce AM, Cho MK. The "how" and "whys" of research: life scientists' views of accountability. Journal of Medical Ethics. 2009; 35(12):762–7. [PubMed: 19948933]

Lakes KD, Vaughan E, Jones M, Burke W, Baker D, Swanson JM. Diverse Perceptions of the Informed Consent Process: Implications for the Recruitment and Participation of Diverse Communities in the National Children's Study. American Journal of Community Psychology. 2012; 49(1-2):215–32. [PubMed: 21671109]

Ludman EJ, Fullerton SM, Spangler L, Trinidad SB, et al. Glad you asked: participants' opinions of re-consent for dbGaP data submission. Journal of Empirical Research on Human Research Ethics. 2010; 5(3):9–16. [PubMed: 20831417]

McCormick JB, Boyce AM, Cho MK. Biomedical scientists' perceptions of ethical and social implications: is there a role for research ethics consultation? PLoS One. 2009; 4(3):e4659. [PubMed: 19252737]

McInnes RR. 2010 Presidential Address: Culture: the silent language geneticists must learn--genetic research with indigenous populations. American Journal of Human Genetics. 2011; 88(3):254–61. [PubMed: 21516613]

Mello MM, Wolf LE. The Havasupai Indian tribe case--lessons for research involving stored biologic samples. New England Journal of Medicine. 2010; 363(3):204–7. [PubMed: 20538622]

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington; 1978. DHEW Publication no. (OS) 78-0012

Public Responsibility in Medicine and Research. Public Responsibility in Medicine and Research (PRIM&R) 2010 [cited February 22 2012]. 2012. The Havasupai Settlement: Implications for HRPPs, IRBs, and Researchers. Available from http://www.primr.org/Conferences.aspx?id=8631

Reverby, SM. Examining Tuskegee: The Infamous Syphilis Study and Its Legacy. The University of North Carolina Press; Chapel Hill: 2009.

Scharff DP, Mathews KJ, Jackson P, Hoffsuemmer J, Martin E, Edwards D. More than Tuskegee: understanding mistrust about research participation. Journal of the National Medical Association. 2010; 21:879–897.

Silberman G, Kahn KL. Burdens on research imposed by institutional review boards: the state of the evidence and its implications for regulatory reform. Milbank Quarterly. 2011; 89(4):599–627. [PubMed: 22188349]

Skloot, R. The Immortal Life of Henrietta Lacks. Random House; New York: 2010.

Tarini BA, Goldenberg A, Singer D, Clark SJ, Butchart A, Davis MM. Not without my Permission: Parents' Willingness to Permit Use of Newborn Screening Samples for Research. Public Health Genomics. 2010; 13(3):125–130. [PubMed: 19602864]

Trinidad SB, Fullerton SM, Ludman EJ, Jarvik GP, Larson EB, Burke W. Research ethics. Research practice and participant preferences: the growing gulf. Science. 2011; 331(6015):287–8. [PubMed: 21252333]

Table 1
Sample questions for IRB chairs from the interview guide

- Please describe your role on the IRB, particularly in addressing genetic research protocols.
- Have you heard of the Havasupai vs. Arizona Board of Regents case?
- [If yes to above], tell me what you know about the case.
- [If yes to above], has the Havasupai case affected the way you review research protocols?
- What are your thoughts on informed consent? On broad consent? On tiered consent?
- Have your thoughts changed as a result of the Havasupai case?

Table 2
Sample questions for researchers from the interview guide

- Please describe your research, particularly any research involving human subjects.
- Have you heard of the Havasupai vs. Arizona Board of Regents case?
- [If yes to above], tell me what you know about the case.
- [If yes to above], has the Havasupai case affected your research?
- What are your thoughts on informed consent? On broad consent? On tiered consent?
- Have your thoughts changed as a result of the Havasupai case?