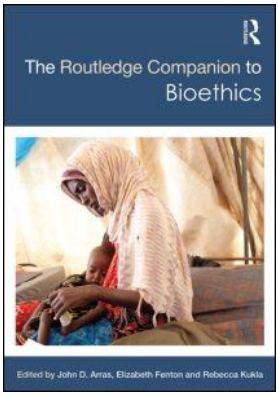

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Ethical Issues In Genetic Research

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ETHICAL ISSUES IN GENETIC RESEARCH

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Introduction

Last week I gave a blood sample as part of research in which I am a volunteer. VITAL is a large study that seeks to learn about the effects of certain dietary supplements. VITAL often asks its subjects to consider "extra" participation, including this blood sample. The blood draw had its own informed consent for the actual procedure and for the use of the information. Interestingly, there is a separate box for me to check to indicate whether I am willing to have the sample used for genetic research.

Why this degree of concern? Why do I give specific consent to genetic analysis of my blood, but not to the possibility that my blood will yield evidence of tuberculosis or gonorrhea? Why is genetic information considered special?

In fact, the question of whether genetic information carries special potential for harm and is thus in need of special protections continues to be controversial. Thomas Murray coined the term *genetic exceptionalism* to describe the belief that "genetic information is sufficiently different from other types of health-related information that it deserves special protection," a view with which he vigorously disagrees (1997: 61).

The claims for genetic exceptionalism include its predictive quality for one's future health, a kind of "probabilistic future diary" (Murray 1997: 62); the relevance of genetic information for one's relatives as well as for oneself; the history of stigma and discrimination associated with claims about genetic traits, leading to everything from forced sterilization to genocide and the Nazis' Final Solution. Other "special" qualities include the way in which research on a small segment of an identified group can confer risk on all members of the group, without their prior knowledge or consent, and the ability to track population migration through genetic research.

Murray's point, however, is that there are very few traits that are entirely genetic (or entirely environmental), and that most of the factors associated with genetic information and genetic research have non-genetic analogs that deserve the same level of protection. Knowing about my cholesterol level and my sky-diving hobby, for example, provides as much of a "future diary" as most genetic information. Murray concludes that genetic exceptionalism is an "overly dramatic" (Murray 1997: 71) view of the significance of genetic information, born of genetic reductionism and genetic determinism. Further, he warns of a "vicious circularity" (Murray 1997: 71): The more we treat genetic information as fundamentally different, the more support we provide for genetic determinism, that is, "the notion that genetics exerts special power over our lives" (Murray 1997: 71).

A common concern regarding genetic research with identifiable populations (such as Ashkenazi Jews or specific Native American tribes) is that information published about the group subjects all members to possible stigma, whereas only a few members actually gave consent and agreed to participate. However, one could raise equal concerns about other forms of research on groups. A sociological study of the sex habits of long-distance truck drivers, for example, potentially stigmatizes all members of that profession, most of whom never gave consent.

One signpost that genetic exceptionalism has won the day is the passage of the *Genetic Information Non-Discrimination Act* (GINA) of 2008, which was strongly supported by research scientists because they hoped it would reassure potential volunteers about participation in genetic research studies. While people may not agree with Dorothy Nelkin and Susan Lindee that the gene has "become the secular equivalent of the human soul" (Murray 1997: 70), we often act as if genetic information is uniquely perilous if it gets into the wrong hands.

History

For millennia philosophers and scientists have been fascinated by the contributions of heredity to human characteristics. Belief in the strength of heredity as opposed to environment (the "nature/nurture" debate) has waxed and waned over the years, but folk idioms such as "chip off the old block" and "the apple doesn't fall far from the tree" all attest to the importance of heredity in the human imagination. Before the Human Genome Project was launched in 1990, it was not possible to look directly at a person's genetic blueprint. Nor can we treat humans like peas or fruitflies, breeding them with mathematical precision in the hope of scientifically useful outcomes. Instead, research on human genetics was, and often still is, a matter of attempting to impose scientific sense on existing family histories. The genetic contribution to alcoholism, for example, was originally quantified through research involving twin, adoption, and family studies. If identical twins had a higher degree of concordance for alcoholism than non-identical twins, or if children whose biological parents were alcoholics had a higher than average likelihood of alcoholism even when adopted by non-alcoholic parents, this was evidence of a genetic contribution to the risk of alcoholism (Foroud et al. 2010).

Most genes are not 100 percent penetrant; most phenotypes are not engendered by only one gene; many genes are pleiotropic, influencing more than one characteristic; most human characteristics result from a confluence of genetics and environment. For example, we now believe that genetic factors account for 50–60 percent of the probable risk of developing alcoholism (Foroud et al. 2010), with the remainder attributable to "environment." Cystic fibrosis, however, is believed to be entirely genetic, with a classic recessive pattern, but with more than 1,800 mutations of the gene, different mutations may account for more or less severe variations of the disease. As these examples attest, genetic research on humans is a complicated business. Research can range from a narrowly focused study of one unique family, to worldwide studies involving thousands of subjects. Genome wide association studies (the search of the genomes of individuals with disease compared with those without the disease) requires thousands of participants in order to arrive at statistically significant results (Rotimi and Marshall 2010).

Because few health states are completely lacking in a genetic component (even a broken leg may reflect an inborn tendency to clumsiness or to risk-taking), genetic research holds out great promise for understanding disease and ameliorating human suffering. More

controversial goals include understanding population migration and the narrative of human ancestry, and prenatal or preconception testing for traits future parents may prefer to avoid. One ethically complex field of study involves behavioral genetics, which seeks to explain human behavior through genetics and genetic–environmental interaction. Claims of genetic components to intelligence, violence, sexual orientation, and so on carry complex societal implications. A society that believed that intelligence was largely due to genetics, for example, would perhaps be more likely to engage in eugenic activities and to spend less on education for "below average" children.

Genetic Research on Stored Tissue Samples

Genetic research is also unusual, although not unique, because it can be carried out without the participation, cooperation, or even knowledge of the research subjects (Clayton et al. 1995). Genetic research can use tissue samples such as blood, saliva, and solid tissue, including samples originally obtained and stored for other uses and from sources long deceased, and also samples shared with researchers pursuing different projects in different institutions.

When scholars in the 1970s were scrutinizing the ethics of research with human subjects and writing the original documents and regulations, the typical research experience involved a time-limited intervention designed to answer a small number of questions. Perhaps the volunteer was asked to take an antibiotic for 10 days, to compare with a comparable drug for efficacy in responding to a specific health problem. Even long-term projects followed participants only until their deaths. The best example is the Framingham Heart Study, which began in 1948 and follows thousands of men and women from Framingham, Massachusetts, looking at factors contributing to cardiovascular disease. The study is now looking at the grandchildren of the original cohort. Although the Framingham questions have changed and expanded over time, participants can stop participating if they no longer want to be part of it. In the traditional research context, participation is active: Subjects typically take a pill or fill out a questionnaire, and if they become disaffected by the research they can end their involvement. However, research using stored biospecimens, while "critical" to understanding genetic variation and its health implications, "challenge[s] the established norms of informed consent" (McGuire and Beskow 2010: 361). Specimens can be stored and used indefinitely, and traded and shared with other researchers working on different questions in different institutions. When specimens are "anonymized," by being stripped of all identifying information, the work is no longer considered to be research with human subjects and falls outside of regulatory protections (Clayton et al. 1995). Thus, research never ends; autonomy rights are limited; future use is unspecified; privacy risks are "uncertain" and persist throughout the subject's lifetime and perhaps beyond; consent is "forever" (McGuire and Beskow 2010).

Privacy is a primary concern for many commentators, and risks to privacy are taken seriously in the practice and regulation of research with human subjects (at least when those subjects are alive). Specimens and research results that cannot be connected to their sources are usually thought to pose little risk. To some people, however, the lack of identifiers is irrelevant, because it is the specimen itself, and not the information obtained from it, that needs to be considered. Many Native Americans would refuse to participate in research if they suspected that their blood specimens would be stored too close to that of a specimen from a taboo clan, breaking the rules against comingling.

Among the Navajo, illness is commonly attributed to the mishandling of specimens separate from the body (Bowekaty and Davis 2003).

Genetic research on stored tissue samples is unusual in that research use can persist long after the source of the tissue is dead. Thus, research on stored tissue has highlighted an old philosophical debate on whether deceased persons can have interests and whether those interests can be harmed.

It is not uncommon for members of minority groups or their advocates to oppose genetic research that they view as threatening the continued existence of their community, e.g., by giving prospective parents the tools to avoid having children with those characteristics. Deaf Pride activists, autistic persons who support "neurodiversity," sexual minorities, and advocates for people with Down syndrome, have all expressed these fears; their interests would be harmed even after their deaths were their specimens to be used in research that threatened to lessen their numbers. Should these beliefs be respected even after these persons are dead?

Federal regulations do not require consent for the use of specimens for research if the specimen is not identifiable or if the subject is dead, although some commentators believe that institutional review board (IRB) review is still worthwhile (Clayton et al. 1995). And yet, I would argue that even dead people can be wronged, and even anonymous specimens can pose risks to the interests of sources both dead and alive. Philosophers such as Joel Feinberg (1984) argue that some interests (for example, in reputation) persist even after death, as do interests in the welfare of one's descendants, and in certain hopes for the future. Feinberg writes "we can think of some of a person's interests as surviving his death, just as some of the debts and claims of his estate do, and that in virtue of the defeat of these interests, either by death itself or by subsequent events, we can think of the person who was, as harmed" (1984: 176). Just as I would be wronged if money that I willed to the Anti-Defamation League were somehow diverted after my death to the Ku Klux Klan (or the other way around!), I would arguably be wronged if genetic researchers discovered and published information about me or my relatives that destroyed my reputation, and to which I would never have consented while alive.

Persons can be wronged if their specimens are used in ways that harm what they perceived to be their interests and values, even if they are not aware of that use. We understand that it would be wrong to use someone's estate to pursue goals inimical to their values. Feinberg (1984) argues that a person would be harmed if some enemy started a whispering campaign that ruined his reputation and humiliated his family, even if his loved ones were somehow able to keep this reality from him, perhaps because he was in a coma. Thus, it can be wrong to use the specimen of someone to pursue research he or she would have opposed when alive, even though, being dead, he or she cannot suffer from that knowledge.

Another way of arguing for this same point is to say that those of us who are now alive and conscious want our own wishes to be honored once we are dead or permanently unaware, and therefore have an interest in protecting the interests of the dead and unaware. Imagine a government with a policy to take organs from all brain dead persons, even those with strong convictions against organ donation. Persons now alive who shared those convictions would oppose the policy, even though it could be argued that they cannot be harmed by what happens to them when they are dead. If I had strong convictions against certain types of genetic research, I would work now to protect myself against contributing involuntarily to that research after my death.

Tomlinson (2013: 42) mounts a strong critique of a research ethics framework that is "all about risk." To protect subjects against risk of harm, we ask their consent for the risk associated with the actual blood draw or biopsy, and the risk to the confidentiality of information garnered from the sample.

> But once a donor to a research biobank has willingly parted with his tissue, and both it and any accompanying medical information have been de-identified, then the donor's welfare is no longer at risk—and she no longer needs any ethical protection. Subject to no risk, she's no longer a human "subject." As for her tissue? It's like her trash. Once left by the curb it's no longer "hers."
>
> (Tomlinson 2013: 42)

Tomlinson believes that respect for donors requires researchers to be transparent about possible future uses of donor tissue, to protect donors against "*nonwelfare* interests in preserving the moral significance of their donation" (Tomlinson 2013: 42). He identifies a number of concerns donors could have about the uses of their gift, including research into prenatal diagnostic testing; research that may stigmatize minority groups; research whose benefits will likely not be justly distributed.

To address similar issues to those Tomlinson raises, Mello and Wolf (2010) support a system of tiered consent. Tiered consent gives donors, at the time of donation, a choice to narrow their gift to this one project, to have their samples used in the future for other health-related projects, to be used only on research on a specific disease, only with additional consent, and so on. Thus, the relatively small percentage of people who want to limit the use of their tissue can do so.

Privacy and Confidentiality

As mentioned above, loss of privacy, or being publicly identified with a genetic trait associated with stigma or discrimination, is a major focus of policy and regulation. Potential research subjects are regularly reassured that their privacy will be protected, and much energy goes into "de-identifying" information. Researchers are required to explain to IRBs and recruits alike, how privacy will be guarded. However, there are a number of ways in which genetic information may elude the protective efforts of even the most conscientious researchers.

Pedigree charts (genetic "family trees") are an efficient and perhaps even an indispensable vehicle for reporting on certain types of genetic research, but the uniqueness of family constellations makes it difficult to protect privacy and confidentiality when pedigrees are published. One can protect privacy by changing details such as birth order and gender, but this is controversial, as it may erode the usefulness of the information. To make matters more complex, a pedigree may threaten the privacy of many family members, but usually only a few people have actually given their consent to be part of the study and to incur that risk. U.S. regulations call for specific written consent of the study subjects when pedigrees are published, but Botkin et al. found that "current practices . . . do not conform with established recommendations and risk the privacy and confidentiality of subjects, often without informed consent" (Botkin et al. 1998: 1808).

Confidentiality can also be threatened by publishing findings about an identifiable group, even though the identities of individuals are adequately protected. Identifying a specific Native American tribe with a high rate of diabetes, or Ashkenazi Jews with

a high rate of a mutation that confers an added risk of certain cancers, may cause at least some members to feel threatened or that their privacy has been invaded (Davis 2000). Of course, opponents of genetic exceptionalism could well point out that high rates of diabetes or cancer in specific groups are public knowledge with or without a genetic narrative.

Finally, the very uniqueness of individual genetic blueprints may render privacy impossible, so that "de-identified DNA" becomes an oxymoron. Although research with de-identified specimens does not currently fall under the umbrella of the Common Rule, McGuire and Gibbs (2006) argue that it ought to do so, given the risk of individual identification from publicly available databases. McGuire and Gibbs recommend required informed consent, with a three-tiered, "stratified" consent process in which participants elect the degree of risk to their privacy with which they are comfortable. However, the authors acknowledge that stratifying consent in this way may create deleterious subject bias.

Community Consent

As we have seen, genetic research may hold out special risks to "socially identifiable populations." These populations might include ethnic groups, indigenous groups, and geographically identified groups. Genetic researchers often focus on small, cohesive groups because genetic traits can be concentrated in groups of people who descended from a small number of common ancestors, the "founder effect." Researchers are especially attracted to groups who have been socially or physically isolated, or who rarely marry outside the group. Even when a group has no higher incidence of a particular trait than the general population, a relatively homogenous population cuts down on background "noise" and can foreground genes of interest. Thus, Ashkenazi Jews, the Amish, Icelanders, and Native American tribes are common foci of genetic interest.

Special risks of genetic research might include undermining the group's creation narrative, challenging the prevailing power structure, or publicizing the results in ways that create stigma or engender discrimination. For example, genetic research that was widely interpreted by lay people to validate the Jewish descent of the Lemba, a South African tribe, resulted in an onslaught of attention from Western Jewish groups, and a shift in tribal culture that challenged the power of existing leaders (Davis 2004). A news headline that drew attention to the high number of "mutant genes" among Ashkenazi Jews, did not sit well with that group of people. Genetics has captured the public imagination, and researchers have no control over how their results are expressed in the popular press.

Because the risks and benefits of genetic research devolve upon the entire "community," while only a relatively few members actively participate and give their consent, some commentators have argued for a type of *community consent* which in its strongest form would give the community a veto over research it deemed unacceptable. A softer form of this argument would require *community consultation* with "recognized cultural authorities" (Weijer and Emanuel 2000). However, even supporters of this view admit that it works well only with indigenous groups, who already have a political structure and relatively clear membership criteria. Critics argue that people who share a genetic heritage are not necessarily a "community" in any social or political sense, and that where communities do exist, they often enshrine the values of subgroups (Davis 2000). (The Lemba, Amish, and Hutterites are examples of groups that are often the subject of genetic research, and whose political leaders are exclusively male. Thus, a "community

consent" from "recognized cultural authorities" would risk ignoring the perspectives of women in the community and would violate the principles of "respect for persons" and "justice" that are two key values of ethical research with human subjects.)

The Havasupai: A Perfect Storm

The long, complicated, and ultimately bitter relationship between genetic researchers at Arizona State University (ASU) and the Havasupai tribe highlights some of the many ways in which genetic research can fall afoul of ethics and the law. The Havasupai are a federally recognized Native American tribe, living in an isolated and stunningly beautiful reservation just west of Grand Canyon National Park. In 2012, the tribe numbered 639 people.

Native tribes have good reason to be wary of genetic research, and a number have described themselves as "just a hairsbreadth away" from shutting it down in their jurisdictions (Bowekaty and Davis 2003: 12). For centuries, white people have dug up the bones and sacred possessions of native people and used them for sale and display. Thus when researchers ask for blood, hair, cheek swabs, or other bodily substances, their requests are framed by this history.

Indigenous peoples are also concerned about "ownership" of their creation stories and communal narratives. Research into tribal origins, such as migration over the Bering Strait, are often met with hostility. Migration studies that can call into question treaty rights or exacerbate tensions with neighboring tribes may pose serious risks to native communities.

Non-Indians who interact with Native American and Alaskan Native people quickly notice the importance of two concepts: Theft and respect (Bowekaty and Davis 2003). Theft has been the primary experience of native people in North America: Theft of land, sovereignty, natural resources, religious and cultural artifacts, children sold into slavery, and so on. In response, respect is a term often voiced by native peoples: Respect for their culture, religion, and values, for their sovereignty, for their sacred artifacts.

There is also a long history of researchers from many disciplines using native peoples as objects of study with little concern for benefiting the people themselves. Genetic research is vulnerable to this criticism, because it can appear to be looking for solutions where the money is, rather than seeking to make the biggest impact on tribal health. Although many tribes struggle with crippling rates of type 2 diabetes, they notice that cheap and proven interventions such as nutrition and exercise programs are often ignored in favor of expensive and highly speculative genetic research.

It is against this background that the Havasupai agreed in 1990 to participate in a genetic study to attempt to tease out some of the causes of the tribe's high rate of type 2 diabetes. In fact, a member of the tribe initiated the collaboration, approaching John Martin, an ASU anthropologist who had a long and mutually respectful relationship with the tribe (Harmon 2010). It is impossible to recount here all the details of this long and sorry story. There was a serious discrepancy between the understanding of tribal members, based on their discussions with the researchers, that the work would be limited to diabetes, and the actual consent form, in which members gave their signed consent to "study the causes of behavioral/medical disorders" (Drybiak-Syed 2010). Martin's colleague, Therese Markow, had initially indicated her interest in studying schizophrenia as well as diabetes, but had been told by Martin that the tribe would not accept that. Confusingly, ASU's IRB gave its approval to a proposal by Markow to study schizophrenia, not diabetes;

in addition, Markow had begun taking blood samples the summer before she received IRB approval. Between 1991 and 1993, recruitment of participants devolved onto Daniel Benyshek, who switched to oral consent only and told participants, apparently in good faith, that the study would focus solely on diabetes. Finally, Markow did not abide by the provisions in the consent form about conducting the research at ASU and keeping "all information" private. Samples were sent to other researchers, other universities, and other countries. Researchers other than Markow had access to codebooks allowing for the reidentification of samples, thus enabling them to look for documentation of schizophrenia among tribal members (Drybiak-Syed 2010).

The Havasupai became aware of what was going on only in 2003, when a member of the tribe (who had herself volunteered for the study) happened to attend a presentation by a doctoral student who had done his work on the tribal samples. When she questioned him about permission to use the samples, the problems began to unfold. Martin asked ASU to remedy the situation by returning the samples to the tribe, but the university refused. Later investigation discovered more than two dozen articles published using the Havasupai samples, on topics including schizophrenia and migration history. In 2004, the Havasupai issued a banishment order, forbidding ASU employees to step onto the reservation; lawsuits were filed against ASU, alleging wrongdoing that had resulted in harm to the tribe as a whole and to individual study subjects. ASU spent in excess of a million dollars in legal fees (Drybiak-Syed 2010).

In 2010, the Havasupai and ASU entered into a settlement, involving return of the specimens; compensation of $700,000; and return of all documents relating to research with the specimens (Harmon 2010). In the wake of this scandal, ASU had an uphill struggle to rebuild trust with its tribal neighbors, and other researchers who were engaged in studies on genetics with southwest tribes had their projects halted. The Havasupai themselves never learned if any of this research held out any hope for their battle with diabetes (Harmon 2010).

Commenting on this case, Mello and Wolf (2010: 206) echo Tomlinson's perspective on "risk," by arguing that "at least some participants consider factors other than individual risk when evaluating future uses of their specimens." But Markow insists that she was merely doing good science, and that her detractors did not understand the peculiarities of genetic research (Harmon 2010).

Conclusion

For every risk of genetic research we can find an analogous risk in some "non-genetic" sphere. In addition, the more we learn about genetics, the more we realize how few conditions are exclusively genetic or environmental. However, genetic research presents a phalanx of ethical issues, often layered within a single piece of research. For that reason alone, genetic research with human subjects deserves the highest level of ethical scrutiny.

Related Topics

Chapter 16, "The Future of Informed Consent to Research: Reconceptualizing the Process," Paul Appelbaum
Chapter 24, "Privacy, Surveillance, and Autonomy," Alan Rubel
Chapter 32, "Reproductive Testing for Disability," Adrienne Asch and David Wasserman

References

Botkin, J.R., McMahon, W.M., Smith, K.R. and Nash, J.E. (1998) "Privacy and Confidentiality in the Publication of Pedigrees: A Survey of Investigators and Biomedical Journals," *JAMA* 279 (22): 1808–12.

Bowekaty, M. and Davis, D.S. (2003) "Cultural Issues in Genetic Research with American Indian and Alaskan Native People," *IRB: Ethics & Human Research* July–August.

Clayton, E.W., Steinberg, K.K., Khoury, M.J., Thomson, E., Andrews, L., Kahn, M.J. et al. (1995) "Informed Consent for Genetic Research on Stored Tissue Samples," *JAMA* 274: 1786–92.

Davis, D.S. (2000) "Groups, Communities, and Contested Identities in Genetic Research," *Hastings Center Report* 30: 38–45.

Davis, D.S. (2004) "Genetic Research and Communal Narratives," *Hastings Center Report* 34: 40–9.

Drybiak-Syed, K. (2010) "Lessons from Havasupai Tribe v. Arizona State University Board of Regents: Recognizing Group, Cultural, and Dignitary Harms as Legitimate Risks Warranting Integration into Research Practice," *Journal of Health and Biomedical Law* 6: 175–225.

Feinberg, J. (1984) "Death and Posthumous Harms," in *Harm to Others*, Oxford: Oxford University Press, 74–95.

Foroud, T., Edenberg, H. and Crabbe, J. (2010) "Genetic Research: Who Is at Risk for Alcoholism?" *Alcohol Research & Health* 33: 64–75.

Harmon, A. (2010) "Indian Tribe Wins Fight to Limit Research of Its DNA," *New York Times*, April 21.

McGuire, A.L. and Beskow, L.M. (2010) "Informed Consent in Genomics and Genetics Research," *Annual Review of Genomics and Human Genetics* 11: 361–81.

McGuire, A.L. and Gibbs, R.A. (2006) "No Longer De-identified," *Science* 312: 370–1.

Mello, M.M. and Wolf, L.E. (2010) "The Havasupai Indian Tribe Case—Lessons for Research Involving Stored Biologic Samples," *New England Journal of Medicine* 363: 204–7.

Murray, T.J. (1997) "Genetic Exceptionalism and 'Future Diaries': Is Genetic Information Different from Other Medical Information?" in M.A. Rothstein (ed.) *Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*, New Haven, CT: Yale, pp. 60–73.

Rotimi, C.N. and Marshall, P.A. (2010) "Tailoring the Process of Informed Consent in Genetic and Genomic Research," *Genome Medicine* 2: 20. Available at: http://genomemedicine.com/content/2/3/20 (accessed July 11, 2014).

Tomlinson, T (2013) "Respecting Donors to Biobank Research," *Hastings Center Report* 43/1: 41–7.

Weijer, C. and Emanuel, J. (2000) "Protecting Communities in Biomedical Research," *Science* 289: 1142–4.