Genetic Research on Biospecimens Poses Minimal Risk

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Abstract

Genetic research on human biospecimens is increasingly common. Yet, debate continues over the level of risk that this research poses to sample donors. Some argue that genetic research on biospecimens poses minimal risk; others argue that it poses greater than minimal risk and therefore needs additional requirements and limitations. This debate raises concern that some donors are not receiving appropriate protection or, conversely, that valuable research is being subject to unnecessary requirements and limitations. The present paper attempts to address this concern using the widely-endorsed 'risks of daily life' standard. The three extant versions of this standard all suggest that, with proper measures in place to protect donor confidentiality, most genetic research on human biospecimens poses minimal risk to donors.

Genetic Research with Human Biospecimens

Advances in biomedical technologies have dramatically increased the scientific value of human tissue and blood samples [1]. As a result, clinicians and researchers now routinely obtain samples and store them for future genetic research. Some commentators argue that this research poses minimal risk [2,3]. Others claim that it poses greater than minimal risk [4]. The persistence of this debate is reflected in the fact that current guidance from institutional review boards (IRBs) and research ethics committees is contradictory. For example, Johns Hopkins states that genetic studies typically pose minimal risk [see: http://www.hopkinsmedicine.org/ institutional_review_board/guidelines_policies/ guidelines/clinical_genetics_research.html], whereas the University of Wisconsin-Madison states that studies involving genetic testing generally pose greater than minimal risk [see: http://kb.wisc.edu/page.php?id=19770]. Studies show that IRB assessments of the risks of genetic research also vary widely [5,6]. Similarly, comments on a proposed genomic data sharing policy from the US National Institutes of Health reveal conflicting views from researchers and the public regarding the risks of genetic research [see: http://gds.nih.gov/pdf/GDS_Policy_Public_Comments.PDF]. Finally, recent findings that donors can be identified by combining research results with information available from other sources [7,8] have raised concern that genetic research on biospecimens may be more risky than was previously believed [9]. Assessments of the risks of genetic research thus continue to be debated [10].

This continuing debate raises the question of whether additional requirements and limitations are needed to protect sample donors, or whether additional requirements and limitations would unnecessarily block valuable research. The present paper addresses this question using the widely-endorsed ‘risks of daily life’ standard [Table 1]. This analysis suggests that, with

standard protections in place, most genetic research on biospecimens poses minimal risk to donors [Outstanding questions box].

The Risks of Genetic Research

The primary risks of genetic research on biospecimens involve potential breaches of confidentiality. In the wrong hands, a finding that a donor is at increased risk for Alzheimer disease might make it difficult for them to obtain employment or insurance. These risks can be reduced by removing all identifying information from the samples. This approach, however, can undermine the scientific value of research samples. De-identifying samples can also prevent donors from withdrawing their samples, and prevent investigators from informing donors of clinically significant findings. To determine whether investigators should remove identifying information, despite these scientific and individual costs, it is important to determine the level of risk that genetic research poses to donors when personal identifiers are not removed.

Research that retains personal identifiers should include standard protections for donor confidentiality (Figure 1). Although these protections reduce the risks of genetic research, they do not make it risk-free. Unauthorized individuals might still gain access to a research database and link the results to individual donors. Donors can also be identified by combining research results with information available from other sources [7,8]. In the US, the Genetic Information Nondiscrimination Act (GINA) provides protection against genetic findings being used to discriminate against donors in specified ways, including denial of health insurance [11]. However, GINA does not address all the ways in which the identification of research findings might be used to harm donors, such as denial of life insurance and long-term care insurance [12].

A second source of risk to donors comes from incidental research findings. These risks are becoming increasingly likely with expanded use of whole-exome and whole-genome sequencing [13]. For example, research on genetic risk factors for cardiac disease might also identify variants correlated with increased risk for breast cancer. Although incidental findings are disclosed only when the potential benefits are thought to justify the risks, disclosure can cause stress, anxiety, or negative effects on donors' self-image [14]. Donors may also undergo risky procedures (e.g. mastectomy) based on incidental findings. The fact that some risks to donors remain, even when standard protections have been implemented, raises the question of whether these risks are minimal or greater than minimal [Box 1].

Genetic Research: Minimal Risk on the 'Risks of daily life' Standard

There is widespread agreement that it is ethically acceptable to expose research participants to some risks in order to collect data to benefit future patients, provided the risks are sufficiently low [15]. Yet, it can be difficult to determine when individual risks are acceptably low: Is an estimated risk to donors of approximately 1 in 10,000 of being denied long-term care insurance acceptable? Or should it trigger additional requirements and limitations, even though they increase the costs of research and may limit what studies can be conducted?

To date, there have been no systematic analyses of the risks of genetic research on biospecimens. As a result, review committees and other stakeholders rely largely on their own intuitions. Unfortunately, intuitive risk judgments are subject to well-documented cognitive biases [16]. For example, we tend to judge unfamiliar activities as posing greater risks than familiar ones. This bias is particularly problematic in the context of research which often involves novel interventions and methods. In addition, intuitive judgments about which research

risks are acceptable vary widely, raising concern that the adequacy of donor protections may vary significantly from site to site, and from IRB to IRB.

To avoid the problems engendered by relying on intuition alone, some regulations direct review committees to evaluate research by comparing its risks to the risks of other specified activities. The most common approach, included in US regulations [17,18], defines research risks as minimal when they do not exceed the risks ordinarily encountered in daily life or during routine examinations [19]. Daily life poses a relatively high likelihood of minor harms (e.g. scrapes and bruises) and a very low – but not zero – likelihood of serious harm. For example, playing soccer poses approximately a 1 in 10,000 chance of complete ligament tear, while the average car ride poses at least a 1 in 1,000,000 chance of death [20]. Under the risks of daily life standard, whether genetic research on biospecimens qualifies as minimal risk or greater than minimal risk depends on whether the risks exceed these and other risks in daily life.

A literature search identified no reported cases in which donors experienced significant harm as a result of their samples being used for genetic research. We did find reported cases of genetic discrimination in the US [see: http://assets.opencrs.com/rpts/RL33903_20070307.pdf]. However, these cases predate the adoption of GINA and did not involve research.

The extent to which an absence of reports of serious harm suggests that no serious harms have occurred depends on the circumstances. Consider first a case in which investigators give an experimental drug to a few research participants and have limited contact with them afterwards. In this case, an absence of reports of harm provides very weak evidence that no harms have occurred. Contrast this with a case in which investigators give a drug that poses a risk of painful peripheral neuropathy to thousands of research subjects, and have contact with them for years.

Here an absence of any reports of harm provides relatively strong evidence that no harms have occurred.

The absence of reports of serious harms from genetic research on biospecimens seems more similar to the second case. Most of the risks posed by genetic research are ones that donors would notice (e.g. being denied long-term care insurance). Moreover, investigators of longitudinal studies remain in contact with donors over time. Hence, if donors were experiencing harms, one would expect at least some of them to be reported in the literature. This conclusion is supported by the fact that instances of genetic discrimination in the clinical setting have been reported, revealing that harms to donors are not being systematically ignored by the literature.

This conclusion is further supported by the fact that at least hundreds of millions of genetic tests have been performed in the research setting. If the risks of this research exceeded the risks of daily life (e.g. 1 in 10,000 risk of moderate harm, 1 in 1,000,000 risk of death), thousands to tens of thousands of donors would have experienced moderate to serious harm by now. The fact that no moderate or serious harms have been reported thus provides relatively strong evidence that the risks of genetic research on biospecimens do not exceed the risks in daily life.

The present analysis suggests that most genetic research on biospecimens qualifies as minimal risk under regulations that use the risks of daily life standard,. Although important, the conclusion that the risks of genetic research on biospecimens are acceptable under many current regulations does not necessarily determine whether these risks are *ethically* acceptable. To assess the ethical acceptability of genetic research on biospecimens, the next two sections evaluate its risks using stricter variations on the risks of daily life standard

The 'Routine Examinations' Standard

Many activities in daily life pose risks that would be excessive in the research setting (e.g. mountain climbing, riding a motorcycle). With this in mind, some commentators propose to limit the 'risks of daily life' standard to the risks posed by routine examinations for healthy individuals [21]. Because the risks of routine examinations for healthy individuals tend to be very low, these commentators argue that this comparison offers a way to evaluate whether the risks of genetic research are acceptably low.

Many healthy adults undergo genetic testing [22], including testing for risks of various diseases (e.g. colon cancer, breast cancer) [23]. Some of this testing, in particular some direct-to-consumer genetic testing, poses inappropriate risks due to inaccurate results and lack of follow-up. The risks of inappropriate direct-to-consumer genetic testing should not be used to evaluate the ethical appropriateness of the risks of genetic research [see: http://oba.od.nih.gov/oba/sacghs /reports/SACGHS_DTC_ Report_2010.pdf; http://www.gao.gov/assets/130/125079.pdf]. By contrast, genetic testing is regarded as posing acceptable risks in several circumstances [24]. For example, at least 64 countries recommend genetic testing for healthy infants [25], and it is estimated that approximately 4 million infants in the U.S. undergo genetic testing every year [see: http://www.babysfirsttest.org/ newborn-screening/screening-facts].

The fact that the risks of genetic testing in the clinical setting are considered acceptable for children is especially important. It is widely agreed that children deserve greater protection in research than adults [26]. Hence, if a given level of risk is appropriate for evaluating the acceptability of the risks of research with children, it should be appropriate for evaluating the acceptability of the risks of research with adults. This suggests that we can evaluate whether the

risks of genetic research are ethically acceptable by comparing the level of its risks to the level of risks posed by genetic testing in the clinical setting.

Comparing the Risks of Genetic Testing in Clinical Care and Research

Research findings are published more frequently than clinical test results. This practice increases the risk that donors might be identified through publicly available information. By contrast, standard protections against breaches of confidentiality tend to be stricter in research than in clinical practice [see: http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf]. Genetic samples and results are available to many more individuals in clinical practice than in research, and they tend to be stored together with the patient's personal information.

Next, a significantly greater number of genes typically are assessed in research than in clinical practice, especially in studies involving whole-exome and whole-genome testing. Research is therefore likely to pose greater risks with respect to discovering and disclosing potentially significant findings. However, it is important to recognize that these findings are disclosed only when the potential benefits to donors are thought to justify the risks [27]. This suggests that the increased risks of disclosure of incidental findings in research typically are offset by increased potential benefits for donors. In addition, as whole-exome and whole-genome testing become more reliable and less expensive, they likely will be incorporated into the clinical setting [28,29]. For example, some commentators predict that, in the near future, whole-genome sequencing may be included in newborn screening programs [30,31].

These considerations suggest that genetic research on biospecimens overall poses similar risks to genetic testing in clinical practice. It follows that the risks of genetic research on

biospecimens qualify as minimal on the stricter 'routine examinations' standard. This conclusion is supported by a second stricter version of the 'risks of daily life' standard.

The 'Charitable Participation' Standard

The risks of most clinical interventions, as well as the risks of many activities in daily life, are justified by the potential benefits they offer to the individuals who engage in them. For example, the risks of vitamin K injections at birth are justified by their potential benefits for the newborn. By contrast, research subjects, including donors to genetic research, frequently face risks without any potential for clinical benefit. This suggests that the risks of many activities in daily life, and the risks of most routine examinations for healthy individuals, may not be the best comparators for assessing the ethical acceptability of the risks of research. Instead, it has been argued that we should evaluate the acceptability of research risks by comparing them to risks that are acceptable in the context of activities designed *to benefit others* [32].

Average individuals face risks from a range of activities designed to benefit others. They drive sick neighbors to the doctor and mow their lawns; they participate in charity soccer games, car washes, and food drives. Similarly, the risks of some routine interventions are justified primarily by the benefits they offer to others. For example, vaccination against Rubella first and foremost protects pregnant women and fetuses.

The risks of genetic research on biospecimens are lower than the risks posed by many charitable activities. Vaccination against Rubella poses risks of serious harms, including seizure and anaphylaxis [see: http://www.cdc.gov/vaccines/vpd-vac/rubella/default.htm#safety]. Similarly, many activities in daily life that are designed to benefit others (e.g. charity food drives and car washes) pose some risks of serious harm to participants. The fact that it is acceptable for

individuals to face these risks in the process of trying to help others suggests that it can be acceptable for donors to face likely lower risks to contribute to valuable genetic research that is designed to benefit future patients.

It follows that most genetic research on biospecimens poses minimal risk. This conclusion suggests that IRBs and other stakeholders should begin with the assumption that genetic research which includes standard protections for donor confidentiality poses minimal risk. IRBs should then consider whether there are any factors present in individual cases that might increase the risks to donors and possibly make the research more than minimal risk.

Exceptions

Population-level risk determinations always admit of exceptions. The claim that a single blood draw is minimal risk does not preclude the possibility that it poses higher risks to some individuals (e.g. those with serious bleeding disorders). Similarly, investigators and IRBs should be aware that, even with standard safeguards in place, some genetic research on biospecimens may pose greater than minimal risk.

In general, the possibility that the risks of genetic research may be greater than minimal arises when the chances of inappropriate disclosure are above average and disclosure could lead to more serious harm for donors. When might these conditions arise [Box 2]? The likelihood of harm may increase when one or more of the standard confidentiality protections cannot be implemented. For example, risks would increase if investigators are not able to limit access to the computer which contains the code to donors' identities. The chances of harm may also increase when these measures are not sufficient to protect donor confidentiality. This might be the case in research on diseases that affect a very small number of individuals.

Possible harms may be more significant for donors who are particularly vulnerable. One example might be research on genes associated with sensitive conditions (e.g. schizophrenia, drug abuse), where testing results could lead to significant harm if obtained by the wrong parties. The likelihood and magnitude of harm may also increase in certain social and legal contexts (e.g. societies with high stigma against psychiatric conditions). When one or more of these factors is present, investigators and IRBs should consider incorporating additional protections and limitations (e.g. further data protection measures, restrictions on sample sharing, removal of personal identifiers).

Concluding remarks

Genetic research on human biospecimens has significant scientific potential. At the same time, it is important to ensure that the donors of biospecimens are appropriately protected. Determining whether and when additional protections and limitations are needed to achieve this goal is made difficult by continuing debate over whether this research poses minimal risk or greater than minimal risk. The present analysis reveals that, with appropriate safeguards in place, most genetic research on human biospecimens poses minimal risk to donors. This conclusion suggests that existing protections should be sufficient and that only in exceptional cases should review committees consider mandating additional protections and limitations.

Table 1: The risk level of genetic research on biospecimens*****

Standard	Definition	Implications for Genetic Research
Daily Life	Risks ordinarily encountered in daily life	Minimal risk: Risks no greater than many daily activities (e.g. playing sports)
Routine Examinations	Risks ordinarily encountered during routine examinations	Minimal risk: Risks no greater than recommended genetic testing in clinical setting
Charitable Activities	Risks ordinarily encountered during charitable activities	Minimal risk: Risks no greater than many activities designed to benefit others (e.g. charity car washes, Rubella vaccination)

***** General risk determinations assume that appropriate safeguards are in place. The claim that a research MRI poses minimal risk applies only when participants' hearing is protected and those with metal in their bodies are excluded. Similarly, the claim that most genetic research poses minimal risk to donors assumes that proper protections are in place to protect their confidentiality.

Box 1. Donor and Community Values

In addition to protecting donors from harm, it is important to ensure that donated samples are not used for research that conflicts with the donors' fundamental values. For example, individuals who fundamentally oppose research on cloning humans should not be made to contribute to such research through the use of their samples. The importance of protecting donors in this regard was highlighted by research on DNA samples obtained from members of the Havasupai tribe that were used to study "theories of the tribe's geographical origins that contradict their traditional stories" [33] thus calling into question donors' culture and identity [34]. To respect the fundamental values of donors and communities, it is important to review proposed studies of stored samples and institute adequate safeguards and protections and, in some cases, to refrain from conducting the research**.**

Box 2. Triggers that might make genetic research greater than minimal risk

Increased chance of harm: unable to implement standard confidentiality measures; small population; readily identifiable individuals

Increased magnitude of harm: few legal protections in place; high potential for stigma

Outstanding Questions Box

1. The present analysis argues that the absence of reports of significant harm experienced by sample donors suggests that genetic research on biospecimens poses minimal risk to donors. Future research might evaluate this conclusion by following a cohort of donors over time and systematically collecting data on any harms they experience. This research also would be valuable for identifying any additional circumstances under which genetic research on biospecimens might pose greater than minimal risk.

2. The present analysis focuses on risks to individual donors. Some genetic research on biospecimens also poses risks to the groups to which donors belong. Because risks to groups tend to be context dependent, IRBs typically should review them on a case-by-case basis, using a process that includes input from members of the groups in question [35]. Future research should consider the level of these risks and appropriate safeguards to minimize them. A method is needed for evaluating what level of group risks is acceptable. In particular, it is not clear how current standards for minimal risk, such as the risks in daily life, might be used to evaluate risks to groups. [For consideration of group values, see Box 1]

Figure 1. Standard protections for donor confidentiality (illustrated)

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