Genotype-driven research recruitment is a potentially powerful tool for studying the functional significance of human genetic variation. With this approach, investigators use an existing study population for which genetic analyses have been conducted to identify individuals who possess a gene variant of interest. Those individuals are then invited to participate in further research involving in-depth phenotyping to better understand the relationship between observable traits and that gene variant. This kind of “recruitment by genotype” eliminates the time-consuming and expensive step of screening new populations to find subjects who have the variant of interest. Such recruitment could be undertaken when investigators want to contact selected participants in their own studies for further research or in the context of biobanks that maintain a link between stored biospecimens and data and identifying information. Conceivably, individuals who have particular gene variants could also be identified by searching across multiple data sets stored in centralized databases, such as dbGaP. This approach could maximize the utility of the massive amounts of data generated in genome-wide association studies, only a tiny fraction of which is related to the disease or condition originally under study.

Genotype-driven research recruitment, however, presents ethical challenges. Concerns about the use and disclosure of genetic information—more commonly associated with participation in genetic research—are shifted to the recruitment phase when genetic information that is generated in one study is used as the basis for identifying and recontacting participants about further research. A central issue is the disclosure of individual genetic research results from the first study as part of the recruitment process for the second. There is a fundamental tension between disclosing genetic research results that may be unwanted and/or preliminary and easily misinterpreted, and leaving prospective participants uninformed about the purposes of the second study and why they are eligible to participate.

Because of the vital role institutional review boards (IRBs) play in reviewing and approving approaches to recruiting individuals to participate in research, IRB chairs are one of the stakeholder groups whose input is essential to
Table 1.
Participant Characteristics (n=100)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years as IRB chair: Mean = 6.7; range = 1–40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>37</td>
<td>(18 )</td>
</tr>
<tr>
<td>≥50 years</td>
<td>149</td>
<td>(74 )</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>129</td>
<td>(64 )</td>
</tr>
<tr>
<td>Female</td>
<td>58</td>
<td>(29 )</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>173</td>
<td>(86 )</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>(2  )</td>
</tr>
<tr>
<td>Black</td>
<td>3</td>
<td>(2  )</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
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<td>(1  )</td>
</tr>
<tr>
<td>Other</td>
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<td>(1  )</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
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<td>(90 )</td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>(4  )</td>
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<tr>
<td>Professional background</td>
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<td></td>
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<td>(41 )</td>
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<tr>
<td>Biological sciences</td>
<td>26</td>
<td>(13 )</td>
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<tr>
<td>Epidemiology/public health</td>
<td>18</td>
<td>(9  )</td>
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<td>13</td>
<td>(7  )</td>
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<tr>
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<tr>
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<td>(2  )</td>
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<td>16</td>
<td>(8  )</td>
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<tr>
<td>Current institution</td>
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<td>(82 )</td>
</tr>
<tr>
<td>Independent IRB</td>
<td>14</td>
<td>(7  )</td>
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<td>11</td>
<td>(6  )</td>
</tr>
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<td>Nonacademic research institute</td>
<td>10</td>
<td>(5  )</td>
</tr>
<tr>
<td>Other</td>
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<td>(1  )</td>
</tr>
<tr>
<td>Familiarity with review of human genetic research</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More familiar</td>
<td>156</td>
<td>(78 )</td>
</tr>
<tr>
<td>Less familiar</td>
<td>45</td>
<td>(22 )</td>
</tr>
<tr>
<td>Ever reviewed protocol involving genotype-driven recruitment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>145</td>
<td>(72 )</td>
</tr>
<tr>
<td>Yes</td>
<td>34</td>
<td>(17 )</td>
</tr>
<tr>
<td>Unsure</td>
<td>12</td>
<td>(6  )</td>
</tr>
</tbody>
</table>

1 May not sum to 100% due to missing data.
2 Respondents were allowed to choose more than one.
3 Includes responses "somewhat familiar," "familiar," and "very familiar.
4 Includes responses "not at all familiar" and "not too familiar.

The development of guidelines on ethical approaches to genotype-driven recruitment. We conducted an online survey to gather data on the opinions, experiences, and concerns of IRB chairs at U.S. institutions that received federal funding for genetics-related research between 2000 and 2010. Our survey focused on whether and under what conditions 1) recontact for the purpose of genetic research recruitment should be allowed, and 2) individual genetic research results from the first study should be disclosed as part of the recruitment process for a second study. In general, our survey included broad questions to establish baseline opinions on these topics, followed by more nuanced questions concerning contextual factors that could potentially modify such opinions.

Study Methods

Sample Assembly. We searched the National Institutes of Health's database of grant awards for new research projects awarded in the period from 2000 to 2010 using the phrase "gene OR genetic OR genome OR genomic." This search resulted in a list of 599 uniquely-named institutions in the United States that had received such funding. We removed institutions from the list (n = 65) that were unlikely to have conducted human subjects research involving genetic analyses (e.g., institutions dedicated to wildlife or agriculture, professional societies).

We attempted to match each remaining institution (n = 534) to an IRB organization (IORG) registered in the United States using a comprehensive roster obtained from the Office for Human Research Protections. For 13 of the institutions, the matching IORG's registration had expired or been deactivated. For 89 institutions, we were unable to identify a matching IORG. To account for the fact that many of these might use a commercial IRB, we
added 30 such IRBs to our sample from a publicly available list. The remaining 432 institutions mapped to 376 IORGs. Because an IORG can operate multiple IRBs, our final task was to identify one chair for each of the 376 IORGs and 30 commercial IRBs to whom we could direct our survey. We e-mailed the Human Protections Administrator at the IRBs with multiple chairs and asked for assistance identifying the chair with most experience reviewing human genetic research. In addition, the survey communications that went to all chairs included the statement, “If you are an IRB chair but would prefer to recommend another chair at your institution who has more experience reviewing human genetic research, please let us know and we will direct our invitation to that person.”

Instrument Development. We drafted our survey instrument based on our knowledge of the issues and literature concerning research recruitment, informed consent, disclosure of individual genetic research results, human research protections, and survey methodology. We revised the instrument based on iterative rounds of comments from all coauthors, as well as on feedback from cognitive pretesting conducted among nine local IRB chairs and senior members.

The final instrument (available upon request) consisted of 40 questions—primarily multiple choice and five-point scale items—and took approximately 20 minutes to complete. The survey included a narrative description and diagram explaining the concept of genotype-driven recruitment. Many of the sections also included a lead-in statement, such as:

Imagine that you have a protocol to review where researchers want to undertake genotype-driven recontact for research recruitment (i.e., they would like to contact the subset of participants in one study who were found to have a particular gene variant in order to invite their participation in a second study to learn more about that gene variant). Understanding that your thinking may change based on the details of a particular protocol, what is your general inclination with regard to each of the following statements.

Survey Implementation and Analysis. We implemented the survey on the Web using Checkbox Survey Software. The survey was fielded in October and November of 2010. Responses were downloaded from Checkbox for descriptive analysis using Stata 11.0. We assessed differences in responses to general vs. scenario-specific questions using Fisher’s exact chi-square tests.

Study Results

Participation Rate. Of the 406 IRB chairs invited, 201 (50%) completed the survey. Most were white, non-Hispanic males, age 50 or older; most reported more than four years of service as an IRB chair and had a professional background in medicine or social science (Table 1). Over 80% chose “academic institution” as the best descriptor of their current institution. Over 75% said they were familiar with the review of human genetic research, and 17% said they had been personally involved in reviewing a protocol involving genotype-driven recruitment.

Acceptability of Recontact for Genetic Research Recruitment.

We asked a series of questions to establish baseline opinions about recontact—not necessarily genotype-driven—for the purposes of genetic research recruitment. There was considerable variation in responses to the general statement “Researchers should be allowed to contact participants in one genetic research study in order to invite their participation in another genetic research study.” Although 37% of chairs agreed with this statement, most either disagreed (27%) or selected “neither agree nor disagree” (36%). These findings suggest that other factors might have an important influence when IRBs are reviewing protocols involving recontact. Indeed, in more detailed questions examining specific aspects of planned recontact:

- 52% said it would be important that the second study focus on the same medical condition as the first;
- 52% said it would be important that the second study involve the same researchers as the first; among those who indicated that it was not necessarily important for the same researchers to be involved (n = 90), 12% said it would be important that the second study at least be conducted at the same institution as the first;
- 91% said it would be important that the possibility of such contact was disclosed during the consent process for the first study; and
- among those who said that disclosures about recontact during the original consent process were important (n = 183), 91% agreed with the statement, “Participants in genetic research should have a choice at the time they consent to one study about whether they are willing to be contacted about other studies in the future.”

In the specific context of genotype-driven research recruitment, a substantial majority of all chairs (90%) again indicated that statements in the original consent form
Box 1. Hypothetical Scenario

Dr. Jones conducted a study to identify gene variants that might be associated with heart disease. She did find one variant significantly more often in participants who have heart disease than in those who do not. However, additional research is needed. Although the gene variant may be associated with heart disease, it is not known how it affects the disease clinically or how it affects the risk of developing the disease in the future.

Thus, Dr. Jones has submitted a protocol to your institutional review board (IRB) for a second study to better understand this gene variant. She proposes to approach eligible participants (i.e., those found in the first study to have the variant of interest) in order to invite them to take part in the second study. She plans to approach them using the method of contact preferred by your IRB.

The original consent form—the one that participants signed for the first study—did not include a statement (either allowing or prohibiting) regarding the possibility of contact about future research. It also did not include a statement (either allowing or prohibiting) regarding disclosure of individual research results.

Excluding respondents who already indicated they “definitely would” allow contact (n = 10), 84% said they would be more likely to allow recontact if the original consent form included the explicit statement, “We may contact you about participating in other research studies.”

Taken together, these results suggest a high degree of consensus that consent disclosures about the possibility of future contact for the purpose of research recruitment are important and highly preferable, but that not all chairs necessarily view them as imperative. This opinion is captured by a comment offered by one chair in an open-ended text box at the end of our survey where we invited chairs to share any additional thoughts:

Autonomy is the most important principle in my opinion. We should give participants the right to be contacted, to know their results, and to participate in future research at the earliest opportunity (i.e., during consent for the original study). If that is not possible, then the decision must be based on other considerations such as the person making the contact, the medium of contact, etc. The latter case is necessarily a more difficult decision, but a blanket disapproval is not warranted, as it not only prevents the advancement of science, but also prevents giving subjects the opportunity to participate in science.

Comments from other chairs, however, demonstrate that some do consider such disclosures essential and may have little tolerance for their absence:

For me the answer depends on whether [participants] were told in the consent for study #1 that they might be contacted again at some future time. If that is not part of the original consent, the researchers would have a very steep slope to climb to convince me they should be allowed to re-contact these people.

If it is so important for future studies, investigators who did not have the simple common sense to ask permission for future contacts can just go out and repeat/extend their critically important research finding that spurs the “need” to contact people based on their private research records.

Disclosure of Research Results in Genotype-Driven Recontact

Similar to the general statement about the acceptability of recontact, there was considerable variation in responses to the general statement, “Each participant should be offered his/her individual genetic results from the first study when contacted about taking part in the second study.” Although 42% agreed with this statement, most either disagreed (21%) or selected “neither agree nor disagree” (32%). This distribution again suggests that other factors may have an important influence on IRBs’ opinions about this issue. When asked:

- 87% of respondents said that statements in the consent form for the first study concerning disclosure of individual genetic research results would be important;
- 86% said that the level of clinical validity of the first study’s findings
Based on responses to the general statement, "Researchers should be allowed to contact participants in one genetic research study in order to invite their participation in another genetic research study." Unfavorable views include those who disagreed or strongly disagreed with this statement; neutral views are those who selected "neither agree nor disagree"; favorable views include those who agreed or strongly agreed.

Based on responses to the scenario-specific question, "Would you allow Dr. Jones to contact eligible participants to invite them to participate in a second study?" Unfavorable views include those who said they definitely or probably would not; neutral views are those who were undecided; favorable views include those who said they definitely or probably would.

would be important (clinical validity was defined as "the accuracy with which the presence of a gene variant predicts the presence of a clinical condition or predisposition"); and

• 76% said that the level of clinical utility of the first study's findings would be important (clinical utility was defined as "the availability and effectiveness of interventions aimed at avoiding the adverse clinical consequences of a gene variant").

We also asked respondents to consider disclosure of research results in the context of the hypothetical scenario (Box 1). In response to this scenario—in which the consent form for the first study did not include any statements either allowing or prohibiting such disclosure, and in which the first study's findings were described as having uncertain validity and utility—42% said the researcher definitely or probably should offer to disclose eligible participants' individual genetic results from the first study as part of her explanation of the purpose of the second study. More, however, either said she definitely or probably should not (28%) or were undecided (22%). This represents a statistically significant departure from responses to our question about the general statement, "Each participant should be offered his/her individual genetic results from the first study when contacted about taking part in the second study" (p < 0.001) (Figure 2). Compared to their responses to this general statement, answers to our scenario-specific question moved in a negative direction (less favorable toward offering results) for 30% of chairs.

We probed about alternative statements concerning the disclosure of results that could have been included in the hypothetical first study's consent form. Excluding respondents who already indicated that the researcher "definitely should" offer individual results (n = 24), 77% were more likely to favor disclosure if the original consent form had stated, "We will offer to disclose your individual genetic research results if they have potential clinical consequences for you and/or your family members."

We also probed about alternative descriptions of the nature of the hypothetical first study's results. One alternative provided an example of findings with limited clinical utility:

Although additional research is needed, it appears that this gene variant conveys a small increase in risk for heart disease compared to that in the general population.
Figure 2.
General vs. Scenario-Specific Views About the Disclosure of Individual Genetic Research Results During the Recruitment Process

At this time, recommendations for people who have this variant would be the same as for the general population: stop smoking, follow a heart healthy eating plan, be physically active each day, and maintain a healthy weight.

This kind of finding did not have a definitive effect: excluding chairs who already indicated that the researcher “definitely should” offer results (n = 24), only 30% said they would be more likely to favor disclosure. A second alternative provided an example of findings with potentially more utility:

Although additional research is needed, this particular gene variant is in a biologic pathway that suggests that, for people who have the variant, diet and exercise alone may not be effective in reducing future risks associated with heart disease. Further, a specific class of cholesterol-lowering drug might be indicated.

This kind of finding was viewed more positively; again excluding chairs who already indicated that the researcher “definitely should” offer results (n = 24), over half (55%) said they would be more likely to favor disclosure.

Taken together, these results again highlight the importance chairs assigned to information conveyed during the consent process for the original study, this time about disclosure of results. They also suggest that, at a minimum, the clinical validity of the results from the original study will be a significant factor in the minds of many chairs when considering whether such results should be offered in the context of genotype-driven recruitment.

Several chairs offered comments at the end of our survey reflecting this opinion:

In general I favor personal autonomy, but I draw the line at informing people about findings whose significance is not clear even to the researchers. It is bad enough that we burden patients with information we believe to be true that later turns out to be wrong. We should not load them with information whose significance is unclear even to us.

I am very reluctant, whether one is dealing with a medical device, a new assay, or genetic test results, to allow the results to enter into real-time decision making. . . . The subject could make decisions based on the results that could place them at risk for additional negative consequences—all because
Table 2. Weighing Ethical Dilemmas

<table>
<thead>
<tr>
<th>When thinking about whether researchers should be allowed to contact eligible participants in the first study about taking part in the second study, which of the following considerations should be given more weight (recognizing that both may be important)?</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protecting participants from unwelcome contact from researchers</td>
<td>103</td>
<td>(51)</td>
</tr>
<tr>
<td>Providing participants the opportunity to hear about research they might like to participate in</td>
<td>60</td>
<td>(30)</td>
</tr>
<tr>
<td>Unsure/don’t know</td>
<td>23</td>
<td>(11)</td>
</tr>
</tbody>
</table>

When thinking about whether participants should be offered their individual genetic results from the first study when contacted about taking part in the second study, which of the following considerations should be given more weight (recognizing that both may be important)?

| Avoiding the disclosure of unwanted genetic information | 98 | (49) |
| Avoiding leaving participants uninformed about why they are eligible for the second study | 72 | (36) |
| Unsure/don’t know | 16 | (8) |

Again when thinking about whether participants should be offered their individual genetic results from the first study when contacted about taking part in the second study, which of the following considerations should be given more weight (recognizing that both may be important)?

| Avoiding the disclosure of genetic information that has uncertain clinical utility | 93 | (46) |
| Promoting participant autonomy to decide for themselves what kind of information they find useful | 79 | (39) |
| Unsure/don’t know | 12 | (6) |

1 May not sum to 100% due to missing data.

they agreed to participate in a research protocol. Placing a subject at avoidable risk “because they agreed to receive the results” is insufficient. The risk versus benefit ratio determination is independent of whether the volunteer states they want to assume the risk, in my view. “Do no harm” and “autonomy” are obviously in tension here. I will always give “do no harm” the right of way.

One chair’s comment serves as a reminder that how results are communicated can be as important as the content of those results:

One concern is whether the participants who are re-contacted and given some form of individual genetic information will be able to comprehend the information accurately. If it is technically precise it may not be comprehensible. If it is stated in layman’s terms, it may be so inaccurate as to give rise to unfounded anxiety. So, I would pay close attention to the manner in which individual genetic information is presented to participants.

Ethical Dilemmas: Weighing the Issues

We concluded our survey by asking directly about the ethical dilemmas involved in genotype-driven research recruitment (Table 2). With regard to whether researchers should be allowed to contact eligible participants in one study about taking part in a second study, more chairs (49%) prioritized avoiding disclosure of unwanted genetic information over avoiding leaving participants uninformed about why they are eligible for the second study (36%).

Finally, in a second dilemma we posed about offering individual genetic results, more chairs (46%) chose avoiding disclosure of genetic information with uncertain clinical utility over promoting participants’ autonomy to make their own deter-
I nvestigations about the usefulness of the information (39%).

Discussion

Identifying and contacting individuals about their interest in participating in research must take place within the context of well-established requirements for ethically responsible research. Even so, research recruitment is typically considered less risky than research participation. When contacted by a researcher, individuals have a number of options, including not responding, expressing disinterest at the outset, or learning more about the research and then making an informed decision about whether to take part.13

Certain approaches to research recruitment, however, involve risks that can rise to the level of harm. Genotype-driven recruitment is one such approach, where potential harms associated with the use and disclosure of genetic information are linked to the offer to participate in research. At the same time, genotype-driven recruitment could significantly advance the pace of research on the functional significance of human genetic variation and speed progress toward the ultimate goal of benefiting human health.14

As a first step toward developing guidelines on ethical approaches to genotype-driven recruitment, we gathered empirical data from one stakeholder group, IRB chairs, about the acceptability of recontact for further research recruitment and the disclosure of individual genetic research results during the recruitment process. The distribution of responses we received to general questions on both of these topics was highly variable and seemed to suggest that the answer may often be “it depends.” This conclusion is further reinforced by the statistically significant differences we found between responses to our general versus scenario-specific questions. A major consequence of these findings is that it is unlikely that there will be a “one-size-fits-all” solution, but rather several approaches to genotype-driven recruitment that may be ethically acceptable depending on a variety of context-dependent factors. Examples of such factors include whether the genotype-driven study focuses on the same medical condition as the study in which participants were originally enrolled, whether it involves the same researchers and/or institution, whether it involves the recruitment of family members, and how and by whom prospective participants are contacted.

Two context-dependent factors in particular generated strong agreement among our survey respondents. First, disclosures made during the informed consent process for the original study are key. Addressing the possibility of future research contact and disclosure of individual results during the consent process—and potentially offering participants choices about these—may help mitigate some of the ethical dilemmas involved in genotype-driven recruitment. Specifically, incorporating these topics into the original consent process is one way of addressing the considerations that IRB chairs selected in our survey as deserving more weight: avoiding unwelcome researcher contact and avoiding disclosure of unwanted genetic information. However, there are several ethical and logistical challenges involved in offering and honoring choices on consent forms,15 and attention is also needed to developing appropriate and easy-to-understand consent language.

The second area of strong agreement that emerged concerned the importance of the clinical validity (and, to a slightly lesser degree, the clinical utility) of the information when deciding whether individual genetic results should be offered during the recruitment process. Issues surrounding the uncertainty and usefulness of genetic research results—together with ethical arguments based on respect for persons, beneficence, paternalism, reciprocity, and the boundaries between research and clinical practice16—fuel the continuing debate over the general issue of whether individual genetic research results should be disclosed to research participants.17

Clinical utility has been the most frequently recommended standard,18 but will likely be difficult to reach in the context of genotype-driven recruitment, where further research is needed specifically because more must be learned to decipher the meaning of genetic research results in terms of risk, inheritance, diagnosis, prognosis, and treatment.19 When choosing the appropriate threshold for disclosure in genotype-driven recruitment, the counterbalancing concern about evasiveness when explaining why prospective participants are eligible must be addressed: If individuals are not offered their individual results, what should they be told about why they are being recontacted? No matter what approach is taken, researchers must be fully prepared to communicate and answer questions in clear lay language about what is known and not known about the role of genetics in their proposed area of research.

In this study, we collected data from a key stakeholder group to inform policy development on a rapidly emerging issue. Other studies of IRB professionals’ views on issues arising in genomic research—such as what constitutes human subjects research, the need to obtain participants’ further consent for new uses of biospecimens, the disclosure of individual genetic research results, and the risks associated with large-scale data sharing—have similarly reported a wide range of opinions.20 This diversity of views may be due in part to a lack of federal regulatory guidance and established IRB policies on some of these new and unresolved questions.21 To help
address the ethical challenges in
the swiftly evolving field of genomics, it may be especially important
for IRBs to have access to a variety of resources, including input from
scientific colleagues, individuals who can articulate the perspective
of research participants, and experts in research ethics.32

Our national sampling frame
and good response rate are impor-
tant strengths of this work.
Genotype-driven recruitment is a
complex topic that we knew would
be novel to most respondents, and
we developed our survey instru-
ment through multiple iterations
and detailed cognitive interviews to
help ensure that questions would be
comprehended as intended and to
to identify answer options that should
be revised or added. Several factors,
however, may limit the interpret-
tion of our results. First, we do not
have data about the characteristics
of IRB chairs who did not respond
to our survey and thus cannot assess
potential response bias; in general,
the demographic characteristics of
our respondents were similar to
those found in surveys of IRBs on
other topics.33 Second, because our
survey comprised primarily closed-
ended questions and was completed
online, we were unable to probe
for even more nuanced views or to
explore other factors that IRB chairs
themselves might have identified as
influencing their opinions. Third,
to constrain the survey to a reasonable
length, we did not include questions
covering every possible issue (e.g.,
whether genetic research results
are produced in a CLIA-certified
laboratory, and the attendant
implications for disclosure to par-
cipants34). Thus, further research
among IRB leaders—perhaps in-
volving semistructured interviews—
is warranted. Input is also needed
from other stakeholders—such as
researchers, research participants,
and treating physicians—for the
development of sound recruitment
policies that protect participants,
yet avoid excessive restrictions that
have a chilling effect on beneficial research.35

Disclaimer
The content is solely the responsi-
bility of the authors and does not
necessarily represent the official views
of the National Human Genome
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References
1. McGuire SE, McGuire AL. Don’t
  throw the baby out with the bathwater:
  Enabling a bottom-up approach in genome-
  wide association studies. Genome Research
2. Beskow LM, Linney KN, Radtke RA,
et al. Ethical challenges in genotype-driven
research recruitment. Genome Research
2010;20:705-709.
3. Chulada PC, Vaidh HT, Sharp RR,
et al. The environmental polymorphisms
registry: A DNA resource to study gen-
etic susceptibility loci. Human Genetics
4. See ref. 2, Beskow et al. 2010.
5. See ref. 3, Chulada et al. 2008.
6. See ref. 1, McGuire and McGuire
2008.
7. See ref. 2, Beskow et al. 2010.
8. See ref. 2, Beskow et al. 2010.
9. U.S. Department of Health and Hu-
man Services, National Institutes of Health.
Research Portfolio Online Reporting Tools
Expenditures and Results (RePORTER).
10. Office for Human Research Protec-
.gov/orhp/assurances/index.html.
11. Citizens for Responsible Care and Re-
search (CIRCARE), Commercial institutional
review boards (IRBs). http://www.circare.org/
info/commercialirb.htm.
12. National Commission for the Protec-
tion of Human Subjects of Biomedical and
Behavioral Research. The Belmont Report:
Ethical Principles and Guidelines for the
Protection of Human Subjects of Research.
Office; 1979.
al. Ethical issues in identifying and recruit-
ing participants for familial genetic research.
American Journal of Medical Genetics Part
2004;130A:424-431; Beskow LM, Sandler
RS, Weinberger M. Research recruitment
through US central cancer registries: Balan-
cing privacy and scientific issues. American
Journal of Public Health 2006;96:1920-
1926.
14. See ref. 1, McGuire and McGuire
2008.
15. National Cancer Institute. Best
practices for biospecimen resources. 2007.
http://biospecimens.cancer.gov/practices/
default.asp; Ram N. Tiered consent and the
tyranny of choice. Jurimetrics 2008;48:253-
284; Beskow LM, Burke W. Offering
individual genetic research results: Context
matters. Science Translational Medicine
2010;2(6):38ec20, DOI: 10.1126/scitransl-
gov/pmc/articles/PMC136874/.
16. Haga SB, Beskow LM. Ethical,
legal, and social implications of biobanks
for genetics research. Advances in Genetics
2008;60:101-144; Dressler LG. Disclosure of
research results from cancer genomic studies:
State of the science. Clinical Cancer Research
17. See ref. 15, Beskow and Burke 2010;
Kohane IS, Taylor PL. Multidimensional
results reporting to participants in genomic
studies: Getting it right. Science Translational
Medicine 2010;2(5):175ec19, DOI:
10.1126/scitranslmed.3000809; Fernandez
C. Public expectations for return of results—
time to stop being paternalistic? American
Journal of Bioethics 2008;8:46-48; Miller


24. See ref. 18, Fals betz et al. 2010.

25. See ref. 2, Beskow et al. 2010.
IRB Review and Public Health Biobanking: A Case Study of the Michigan BioTrust for Health

After three years of preparation that included input from scientists, business leaders, and the general public, the Michigan BioTrust for Health was inaugurated in June 2009. The BioTrust is an initiative that makes available to researchers dried blood spots left over from state-mandated newborn screening. These blood spots were originally obtained from newborns for a clinical purpose: to screen for certain metabolic and genetic conditions that are treatable if detected early. The dried blood spots are stored in the Michigan Neonatal Biobank, a nonprofit organization that jointly manages researchers’ access to the samples with the Michigan Department of Community Health (MDCH). The MDCH is the agency with jurisdiction over the state’s newborn screening program. As such, its institutional review board (IRB) faced several novel questions regarding the IRB’s role in reviewing research using materials from a biobank created by the state. They included questions about community and individual interests at stake in biobanking, as well as questions about the relevance of parents’ goals for permitting their child’s blood spots to be in a biobank and their interest in protecting personal rights. These issues encapsulate in microcosm general ethical challenges for biobanking that loom large for the research enterprise as the number of biobanks and the recognition of their research potential increase.

The MDCH IRB answered these questions in ways that 1) recognize that contributing biospecimens to a research biobank is itself participation in research and thus in need of IRB oversight, even if the primary purpose of collecting the biospecimens was clinical; 2) affirm the need for IRB review and approval of specific studies using residual newborn screening blood spots; 3) require informed consent for the potential research use of newborn screening blood spots from this point on, while allowing the IRB to consider waiving the requirement for parental permission (informed consent) when previously collected blood spots have been deidentified; 4) recognize community, not only individual, interests at stake; 5) acknowledge that both individuals and groups may have interests beyond confidentiality that rightly should be considered in biobanking oversight (such as concerns that the goals of research be consonant with the sample donor’s personal values, or attention to vulnerabilities of certain social groups), and 6) incorporate the results of community engagement in its decision-making. The story of the Michigan BioTrust for Health provides evidence that each of these ethical tenets can be implemented by other biobanks and their reviewing IRBs.

Background of the Michigan BioTrust for Health

The dried blood spots in the BioTrust were originally collected for, and will continue to be collected for, clinical purposes: the screening of Michigan newborns for metabolic and genetic diseases immediately after birth. Newborn screening does not require parental consent in Michigan, given the potential benefit to the newborn. Birthing hospitals and midwives are required to provide this screening. Parents may decline newborn screening only through a self-initiated opt-out, which is rarely pursued.

Michigan has a comprehensive archive of residual newborn screening blood spots for idiosyncratic historical reasons. In 1984, the state began saving blood spots left from newborn screening for 21.5 years pursuant to a state attorney’s recommendation to keep each newborn’s residual blood spots until s/he reached the legal age of adulthood. This was done in case the blood spots were needed for personal clinical or forensic use—a situation that rarely arose. When the state began saving residual blood spots in 1984, the
research potential of these materials was not considered. In 1999, the gubernatorial Michigan Commission on Genetic Privacy and Progress recognized the research potential of the stored newborn screening blood spots. It recommended that the state store blood spots indefinitely, not only for personal use but also for possible medical research. Following that recommendation, the state legislature enacted a law allowing research on stored blood spots, subject to the ethical constraints of the Common Rule, the federal regulations governing research with humans. The result is that Michigan now has almost four million stored blood spots potentially available for research representing statewide birth cohorts from 1984 to the present.

Michigan’s proactive attempts to address the ethical issues that research with residual newborn screening blood spots raises occurred during the time that highly publicized citizen lawsuits against such research emerged in Minnesota and Texas. In those states, parents alleged that their rights were violated because newborn screening blood spots were retained, and research was conducted on them without parents’ consent. The state governments argued that parental rights were not violated because the deidentification of the blood spots adequately protected privacy interests. As the Minnesota case proceeded through multiple levels of the state court system, public health officials worried that the publicity might undermine parental support for clinical newborn screening, thus possibly endangering children’s health. However, to date, the number of parents in Minnesota who opted out of clinical newborn screening has increased only marginally. As part of the settlement of the Texas lawsuit, the state was required to destroy more than four million stored blood spots.

Before the BioTrust was developed, deidentified blood spots left over from Michigan’s newborn screening program were used in 10 studies without the knowledge or consent of the parents of the children whose samples were provided to researchers. The MDCH IRB determined that according to the Common Rule, because the existing samples were deidentified, the research did not involve human subjects and therefore did not require parents’ consent for use of the blood spots in research. The regulatory exception to consent is based on the assumption that when researchers obtain deidentified biospecimens, there is little risk that the individuals from whom the materials were obtained would be harmed by the research. Because of the deidentification process, the possibility of identifying individuals whose biospecimens were stored was deemed negligible.

IRB Review and the Intent to Conduct Research

The development of the BioTrust introduced new considerations for the MDCH IRB. Up to this point, blood had been collected and stored for purposes related to newborn screening and for possible personal use. However, Michigan law permitted residual newborn screening blood spots to be used incidentally for research. The BioTrust was developed to make the residual dried blood spots intentionally available to researchers, including researchers outside the MDCH. While promoting health research is the primary goal, the BioTrust also explicitly endorses secondary economic benefits that may come from a biobank facilitating research on residual blood spots. The hope is that more deliberate research use of the blood spots will result in a financially self-sustaining storage facility, and that in the long run the BioTrust will contribute to the development and growth of Michigan’s biotech sector.

The key question the IRB faced was whether this change of intent for the storage and use of residual dried blood spots should change the review paradigm regarding research with the materials. The IRB concluded that it should. The IRB determined that research use of blood spots stored in the BioTrust required informed consent, or a waiver of informed consent for those blood spots that had been collected in the past. Thus, a new process would have to be developed to seek informed consent from parents. The use of the blood spots collected in the past would depend on IRB consideration of whether the general conditions for a waiver of informed consent were met. Furthermore, the IRB emphasized that all studies proposing to utilize the blood spots should be reviewed by an IRB. (IRB discussion focused on the use of deidentified blood spots, since use of identified blood spots has always required study-specific consent.)

The IRB considered both theoretical and practical issues in coming to this conclusion. It understood the primary question to be “What is right?” regardless of how federal regulators interpreted the Common Rule regarding research with stored, deidentified biospecimens. Ultimately, the IRB rejected one proposed view—that the existing blood spots were medical waste that could be used freely in a deidentified form. That view conflicted with increasing evidence that parents want researchers to ask for permission to use their child's
newborn screening blood spots for research, particularly for genetic studies. Indeed, both the controversies in Texas and Minnesota and a national survey conducted concurrently indicated that many parents feel permission is morally required.4

Given the double-coding process for deidentifying blood spots, the IRB judged the possibility of a privacy breach to be very low. Public health data to which the blood spots might be linked in research studies, such as data from cancer or birth defect registries, is similarly deidentified. But the IRB recognized that some parents might think they have interests beyond privacy considerations when newborn screening samples are used in research. For example, the state's goals for research might not match parents' priorities for publicly supported research. Moreover, some parents might be concerned that the blood spots would be used in kinds of research that contravenes their values.5 Thus, the IRB felt that given newly galvanized research intent for residual blood spots, obtaining parents' consent was consistent with the principle of respect for persons in the Belmont Report6 and therefore the right thing to do.

As a practical matter, the IRB considered potential effects that newly encouraged research with residual blood spots could have on the clinical newborn screening program. The IRB deemed it crucial that research interest in the blood spots not jeopardize the primary purpose for collecting blood from newborns: disease screening that demonstrably benefits them. Health officials in Minnesota and Texas expressed fear that belatedly discovered research could result in negative public reaction against newborn screening. The IRB recognized that public education intended to create a meaningful right of refusal for research also might inadvertently cause negative reaction to newborn screening, especially given that few Michiganders have realized that blood from newborn screening is saved and may be used for research. People disconcerted to learn of potential research use might become uncomfortable with newborn screening. For example, the explicit request to consent to research might make new parents question why they were not asked for their consent to take blood from their child in the first place. The IRB recognized the importance of making clear the distinction between clinical newborn screening and the research use of residual blood spots in all efforts to enable citizens to participate in or withdraw from the BioTrust initiative.

In its deliberations the IRB explicitly considered findings from public engagement activities about the BioTrust. State officials had encouraged preliminary public engagement sessions before implementation of the BioTrust, both because they recognized the potential for parents' confusion about the largely unknown archive of residual blood spots, and because they realized some parents might be uncomfortable with a state-sponsored biobank that contained their child's blood spots. Preliminary engagement sessions conducted by state officials and by academic and nonprofit partners within Michigan mirrored new national findings about consent for research with biospecimens: many Michiganders said they should be asked for permission for researchers to use their biospecimens or their children's newborn screening blood spots in research.7 Moreover, some participants in the engagement sessions expressed concerns about the BioTrust that went beyond confidentiality—concerns that the protections of deidentification were insufficient to redress. They expressed concern about potential differentials in group harms and group benefits, which goals of research would be prioritized, and who would represent “the community” in making those research choices.

In the course of its deliberations, the IRB also sought guidance from the Department of Health and Human Services' Office for Human Research Protections (OHRP). In personal correspondence replying to the IRB, OHRP clarified that it considers contributing a tissue sample to a research biorepository an act of research participation. The consonance between its deliberations and OHRP's clarification cemented the IRB's conclusion: informed consent8 or a waiver of consent was required for the research use of stored residual blood spots that the BioTrust would make available to researchers. That conclusion in turn influenced the MDCH's commitment to develop a process for obtaining informed consent for research with blood spots collected in the future, and discussions by the BioTrust's Community Values Advisory Board related to this.
Informed Consent for Research with Blood Spots Yet To Be Collected. The IRB determined that for research with blood spots to be collected in the future, researchers would need to obtain parents' consent. This new consent requirement involves an "opt-in" consent process to meet the full criteria of informed consent. While some states have recently developed explicit "opt-out" systems for use of leftover blood spots in research, the MDCH IRB determined that an opt-out approach does not constitute full informed consent because consent is presumed and because the regulatory standard is for consent—i.e., opting in—or its formal waiver, rather than opting out.9

In concordance with the IRB decision and the values of its members, the BioTrust's Community Values Advisory Board made developing a consent process for research use of newly collected blood spots a first priority of its mission. With guidance from the Community Values Advisory Board, the MDCH implemented an informed consent process in all of the state's birthing hospitals by the fall of 2010. This effort required developing new educational materials that explicitly differentiated newborn screening (which remains mandatory in Michigan) from donation of the residual blood spots to a research biobank. The documentation form for the consent process includes specified "yes" and "no" answers to the question whether a parent wishes the child's stored residual blood spots to be available for potential use in research. Only the blood spots of parents who check "yes" can be used for research. A blank form will be interpreted as a "no." Michigan became the first state in the country to require explicit permission from parents for research with residual newborn screening blood spots.

Conditional Waiver of Consent for Research with Preexisting Stored Blood Spots. The IRB recognized the practical infeasibility of obtaining explicit consent for the four million archived blood spots to be made available for research. However, its decision that general informed consent regulations apply meant that the archived, deidentified blood spots could be used for research only if the Common Rule's four conditions for granting a waiver of informed consent were met: 1) the research involves no more than minimal risk to the subjects, 2) the waiver will not adversely affect the rights or welfare of subjects; 3) the research could not practically be carried out without the waiver; and 4) when possible, subjects will be provided with information after participation. The IRB granted a waiver for use of deidentified existing blood spots on those terms, subject to annual review for renewal. However, by the logic of the fourth waiver criteria, the IRB determined that a renewal of the consent waiver would depend on good-faith public education about the existence of the residual blood spots, the state's intent to use them, and an individual's right to forbid possible use of her stored blood spots in research. (Those individuals could be either parents of minors with blood spots in storage, or adults whose blood spots were stored when they were babies.) Currently, then, Michigan requires parental consent for possible research use of their child's blood spots and allows a parent or an adult who was screened as a newborn to exclude blood spots that are already archived from possible research use.10

Requirement for IRB Review of Research Proposals. The IRB did not equate a waiver of informed consent for the archived blood spots with a waiver of IRB review of proposals for research with residual newborn screening blood samples. On the contrary, it concluded that mandatory IRB review of all proposals for research with residual blood spots is all the more important because of the potential to waive the regulatory requirement for consent. Because newborn screening blood samples were obtained before a research biobank for residual blood spots was envisioned, parents did not have the chance to consider the risks and benefits of research with their child's blood spots. Thus, the IRB considered it crucial for a body charged with attending to the rights and welfare of research participants to weigh the risks and benefits of every research proposal, including those using only "consented" blood spots, for parallel reasoning. Although parents now give permission for future research with their child's residual blood spots, they do not have the chance to assess the risks and benefits of specific studies in which their blood spots might be used.

The IRB also deemed that mandatory IRB review was important because group as well as individual risks and benefits should be taken into account. In the national context, the legitimacy of group concerns was highlighted by the contemporaneous litigation that the Havasupai Indian tribe pursued against Arizona State University.11 The Havasupai felt deeply wronged that deidentified tissue samples they had provided with one intent (diabetes research) were then used for research with other goals (schizophrenia and tribal origin research) that could threaten their tribe with social stigmatization or with an outside challenge to their tra-
ditional story of tribal origin. Within Michigan, some participants in the citizen engagement sessions had expressed concerns that various social groups might be differentially benefited or burdened by BioTrust research. Thus, the IRB felt that the spirit of respect for persons demands going beyond the “letter” of regulatory requirements that focus on individual risk to consider potential group harms.

New Institutional Partnerships to Protect Individuals and Communities

Through its decision-making process, the MDCH IRB became a constructive partner in a pioneering state effort to obtain public support for public health-related biobanking and to develop a consent process for parents whose children’s residual newborn screening blood spots would be stored for future research. That multipronged effort included other stakeholders, including the MDCH, the BioTrust, the Community Values Advisory Board, academics, and leaders from nonprofit organizations. The IRB’s recognition of community and individual stakes in the BioTrust dovetailed the state’s legal analysis of ownership of the blood spots. A state roundtable on the question of ownership concluded that the state had “qualified ownership” of the blood spots—qualified, that is, by fiduciary responsibility to the community. Implicitly, the state endorsed a charitable trust model of public health biobanking. Institutionally, that resulted in the incorporation of the Michigan Neonatal Biobank as a separate 501(3c) nonprofit organization under state stewardship. The BioTrust contracts with the Michigan Neonatal Biobank to store dried blood spots and process them for research.

Establishing a Community Values Advisory Board for the BioTrust composed of members nominated by diverse community groups provided an infrastructure for community oversight. In a mutually informative process, the IRB has reported to the Community Values Advisory Board proceedings and findings in relation to the BioTrust and has also solicited input from the Community Values Advisory Board regarding the development of ethical guidelines for the BioTrust. The IRB also agreed to solicit input from the Community Values Advisory Board in the future regarding research proposals that merit special public oversight—for example, in cases in which research might pose minimal risk to individual subjects but more so to populations, or in which specific groups might have moral objections to certain kinds of research. In effect, the IRB recognized that the calculation of research risks and benefits for public health biobanking could not be approached simply as a sum of individual risks and benefits, and thus that meeting the traditional charge of an IRB required new institutional collaborations.

The BioTrust is just beginning to receive and evaluate proposals for research with the blood spots. The experiment of this public trust will be shaped in part by the IRB’s decisions: that respect for persons necessitates consent for tissue donation to a research biobank and that risk/benefit calculations for public health biobanking require consideration of group as well as individual risks and benefits.

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References

1. In the 2009 district court case, the judge dismissed the plaintiff’s motion that research on deidentified residual blood spots without consent violated the plaintiff’s privacy rights, including but not limited to privacy rights specifically granted by Minnesota’s Genetic Information Act (Bearder et al. v. Minnesota, No. 27-CV-09-5625). In 2010 the district court judgment was upheld by the Minnesota Court of Appeals. In November 2011, the Minnesota Supreme Court ruled that an actual blood sample meets the definition of “genetic information” under the state’s Genetic Information Act of 2006 and thus is entitled to special privacy protections. The Court remedied the case to the district court to determine whether any of the parent appellants had established the fact that a violation regarding the use of their children’s residual dried blood spots had occurred (i.e., that their children’s residual dried blood spots had actually been used in research without their knowledge), and if so, whether they are entitled to remedies (Bearder v. State of Minnesota et al., A10-101, November 16, 2011).


7. Initial public engagement sessions specifically on the Michigan
BioTrust included a citizens' deliberative process sponsored by Michigan State University; a series of four public library forums conducted by the Life Sciences and Society Program, University of Michigan School of Public Health; outreach to the University of Michigan community sponsored by its Center for Ethics in Public Life; a series of regional focus groups conducted by staff members from the Michigan Department of Community Health; and a community forum sponsored by the Flint-based nonprofit organization Community-Based Organization Partners. See Fleck L, Mongoven A, Marzec S. Stored blood spots: Ethical and policy challenges, http://www.ippsr.msu.edu/Publications/HPFleck.pdf.

8. The language of “consent” can be problematic in biobanking contexts because the research that will be pursued is unknown future research. At the time a biospecimen is contributed to a biobank, it is difficult to speculate about risks and benefits of research in ways that can be done when people volunteer to participate in a specific research study. In reality, biobank donors are giving permission to an institution to make decisions about future research use. However, in this essay we employ the conventional language of informed consent because the IRB sought to fulfill the spirit of informed consent as much as possible in its approach.

9. Ellis G. Informed consent—legally effective and prospectively obtained. Memo from U.S. Department of Health and Human Services Office for Protection of Research Risks. August 12, 1993. States developing opt-out processes may not consider full informed consent necessary because they may not consider providing the biospecimen for storage to be an act of research, but rather see the biospecimen only as an artifact of primary clinical use. In other words, they may not consider their blood spot archives to be research repositories, subject fully to human subjects regulations. Implicitly, the MDCH IRB questioned whether this position can continue to be maintained as research interest in residual blood spots increases nationally. Explicitly, the IRB found that the stated research mission of the BioTrust made such reasoning inapplicable in Michigan’s case.

10. These requirements are sometimes summarized as “opt-in for new blood spots and opt-out for old.” But technically the IRB did not consider the right to exclude one’s previously archived blood spots from research as an “opt-out.” Because ethically informed consent is needed, the de facto opt-out format was a result of waiver conditions for informed consent being met in this case. It was a concession to feasibility concerns under conditions of minimal risk, not an endorsement of opt-out strategies as a defensible substitute for informed consent.

11. Harmon A. Indian tribe wins right to limit use of its DNA. New York Times, April 21, 2010. Two legal cases, one filed by an individual Havasupai and one by the tribe, became consolidated in multiple layers of court review. Tilousi v. Arizona State Board of Regents; and Havasupai Tribe v. Arizona State University Board of Regents, 204 F.3d 1063 (9th Circuit 2008).


Informational Risk, Institutional Review, and Autonomy in the Proposed Changes to the Common Rule

In 2011, the U.S. Department of Health and Human Services (HHS) proposed changes to its regulations governing research with humans (the Common Rule), which apply to all federally funded research. The proposed changes represent a valuable step in updating regulatory protections for research participants to reflect challenges that have arisen over the last 30 years. Efforts to streamline the research review process by shifting the attention of institutional review boards (IRBs) to the riskiest research and away from low- to minimal-risk studies are necessary in order to reduce unnecessary regulatory burden and to more efficiently expend limited institutional resources.

A key feature of the proposed regulatory change is to have the Health Insurance Portability and Accountability Act's Privacy Rule (HIPAA Privacy Rule) serve as the policy for protecting research data. Standardizing how data are protected is, on the face of it, a rational and efficient change. As it now stands, there are multiple approaches that vary between the clinical and research settings and that generate additional inefficiency and friction along the already blurred lines between research and treatment. However, it is dangerous to conceptualize risk as largely restricted to the economic or social consequences of having one's private data made public, or even to the breach of privacy from the release of health-related information alone. We argue that there are negative consequences to adopting the HIPAA Privacy Rule's narrow focus on informational, rather than participatory, risk to research participants.

As a clinical standard, the HIPAA Privacy Rule conceives of risk to the individual as stemming exclusively from the inadvertent or unwilling release of a patient's protected health information. Moreover, the Privacy Rule is based on the assumption that by signing an authorization permitting the use and disclosure of their protected health information, individuals have agreed to accept the risk of any harm that flows from disclosure. The idea that risk and harm to research participants are limited to the release of information is reflected in the proposed changes to the Common Rule. For example, the proposed rule would remove the need for ongoing consent from research participants as long as their personal information is maintained in a secure fashion and not returned to them. Thus, biospecimens collected for one study will be available for use in any other study, provided blanket consent for their use has been provided. Ironically, adopting the HIPAA Privacy Rule's view of risk would exacerbate divergence with the Common Rule because the two rules treat blanket consent differently: whereas blanket consent for biobank research with identifiable information is permitted under the Common Rule, it is prohibited by the HIPAA Privacy Rule.

A second example of the focus on informational risk is the proposed rule change affecting social and behavioral research. The proposed changes would remove the need for IRB review of studies using specific social science methodologies even if information is potentially damaging to the individual and is stored in an identifiable way. The implication is that certain behavioral research methodologies—including surveys, interviews, and focus groups—cannot generate risk as long as the participants are competent adults. Any informational risk that may result from such studies is assumed to be covered by compliance with the standards of the HIPAA Privacy Rule.

It may be true that the primary concern of most individuals who participate in research—particularly when that participation involves the collection and storage of biospecimens—is to avoid stigma or discrimination adhering to the release of incidental informa-
tion about their health status or that of their family members. But this is not the only concern. As the recent court settlement in the case Havasupai Tribe v. Arizona Board of Regents demonstrated, some research participants have serious concerns about the use of their biospecimens that are not limited to the release of identifiable information. In this case, the Havasupai tribe sued the University of Arizona for permitting the use of individual tribal members' stored DNA samples in studies of schizophrenia and ancestral migration. The Havasupai were concerned not just that their tribe may have been identifiable based on supposedly anonymized biospecimens and data, but that their biospecimens had been used, without their consent, for research that ran counter to important cultural and religious tribal values. Likewise, many parents have raised objections in several lawsuits to research with their child's residual newborn screening blood sample without their consent. They claim that without consent, research with their child's sample violates parents' right to control the use of their child's biospecimens.

We argue that there are negative consequences to adopting the HIPAA Privacy Rule's narrow focus on informational, rather than participatory, risk to research participants.

The proposed changes to the Common Rule do not address these problems. Instead, they suggest that the acquisition of blanket consent on collection would permit unlimited use of biospecimens and data for all possible projects. But the effectiveness of blanket consent is contested. As with the Havasupai tribe, many individuals give biospecimens to a specific research project and assume that research with their biospecimens will be limited to that project. Unless individuals have sophisticated knowledge of scientific research, they will be unable to conceive of every possible use of their biospecimens and cannot give informed consideration to whether they are willing to provide their biospecimens for any type of research. At least on a philosophical level, it is possible to violate an individual's autonomy even if he or she is unaware that the violation has happened, and that it runs counter to the ethical principle of respect for persons.

A further unintended consequence of the proposed regulatory changes is that removing IRB review from studies that do not intend to return individual results to participants creates a strong disincentive to do so. If researchers are given a choice between designing a protocol that returns results and one that is excused from the IRB review process, it seems clear where the incentives lie. In the long term, one can imagine a situation in which a majority of genomic research projects return no results to their participants even if those results reveal information that has life-threatening consequences and are clinically actionable. Creating such incentives runs contrary to the emerging consensus in the research and policy community; several groups have concluded that researchers may be obliged to return at least some results, especially those that may have direct health benefits.

Restricting conceptions of risk to the informational is also problematic in the context of social and behavioral research. Under the proposed changes, as long as social and behavioral research is conducted with "competent adults" rather than vulnerable populations, researchers could register their studies in an existing database without having those studies reviewed by an IRB. These proposed changes are based on the idea that such research uses methods that do not pose a physical risk to participants, as do clinical drug and device studies. The risks of social and behavioral research are more likely to be tied to the content or structure of the research, which may involve deception or public observation. For instance, the well-known Tearoom Trade study, in which a researcher posed as a member of an underground homosexual community in order to observe its members' behavior, is considered highly controversial despite the fact that the behavior in question took place in a public place, and no identifying information about the participants was revealed. However, even if the identities of the individuals observed in the study were not reported, it is questionable whether respect for their privacy was upheld.

Under the proposed regulations, it seems possible that research like the Tearoom Trade study would not even undergo IRB review. One response to this scenario would be to insist that individuals who enroll in all social and behavioral research give consent to participate. While this would address the use of face-to-face deception in studies using interviews and surveys, it would curtail public observation research for which requesting consent is either impossible or creates an insurmountable observation bias. Instead, we recommend that all studies meeting the criteria for the new minimal-risk category undergo review and validation.
by an appropriately trained IRB staff member to ensure that the criteria for minimal risk are met.

For social and behavioral research, validation of minimal risk should cover the proposed content of the research and the recruitment methodology. Studies that involve the use of deception or discussion of psychologically disruptive topics—including the realization of adverse health risk or status; the experience of significant trauma (where trauma is defined as the onset/event of severe injury or disability, the death of a family member, interpersonal violence, or abuse); or the experience of severe stigmatization, persecution, or discrimination—should be referred to the IRB for review. This approach would require the appropriate training of a small number of staff to recognize and evaluate participatory risk. The far more resource-intensive alternative is to train thousands of researchers who may not have an incentive to accurately recognize when their proposed research constitutes minimal risk.

In general, we feel that the changes proposed by the HHS represent a step forward for human subjects research review. Several provisions will provide highly desirable streamlining of the review process and remove unnecessary barriers to the efficient conduct of research. However, we feel that it is necessary to ensure that the push for efficiency does not supersede the need for IRB review or lead to a narrowing of the definition of risk that emphasizes privacy at the expense of autonomy.

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References


ERRATUM

In the January-February 2012 issue, the name of one of the coauthors of “Clarity and Appeal of a Multimedia Informed Consent Tool for Biobanking” was spelled incorrectly in the byline and citation. The correct spelling is Jeanette T. Benson.
IRB: Ethics & Human Research is a peer-reviewed journal that publishes scholarly articles offering insight on issues of critical importance to research with human subjects, including findings and analyses of empirical studies. Article manuscripts are typically 3,500 words (text, references, tables, and figures), though we welcome longer and shorter pieces. We also welcome brief commentary (1,000-1,500 words) and letters to the editor (800 words). All references in articles and commentary should be to the most pertinent and up-to-date sources; letters to the editor should not have references.

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