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Genetic Research with Stored Biological Materials: Ethics and Practice

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Many biomedical advances—particularly advances involving genetics—have only been achieved through research with human biological materials.[1] Such research has been critical in identifying genes and gene changes associated with disease or disease susceptibility,[2] determining causes of mortality and morbidity,[3] deriving cell lines for further research,[4] and developing new approaches to therapy such as pharmacogenetics.[5] Complete mapping of the human genome and improved ability to conduct genetic and genomic analyses expand enormously the potential value of biological materials for medicine and science.[6]

Although scientifically rewarding, genetic research with stored biological materials raises several ethical concerns. DNA obtained from stored biological material is stable and specific to an individual; furthermore, genetic/genomic test results have become easier to link to specific individuals, even among pooled DNA.[7] Genetic testing may reveal information about individuals'—and, in some cases, their family members'—present and future susceptibility to illness.[8] Moreover, individuals may not even be aware that their biological materials were collected and stored for future research.[9] Even when individuals gave explicit consent for research with their biological materials, concerns have been raised about the validity of such consent for use of the materials in future, unspecified studies.[10] Finally, whether and under what conditions research results should be disclosed to research participants raises concerns about potential psychological harm to individuals, as well as to groups, if findings create or reinforce negative stereotypes about socially identifiable groups, and about the clinical validity and utility of genetic information obtained in the research context.[11]

Several advisory commissions, government bodies, professional organizations, and commentators have issued recommendations and guidance regarding the collection, storage, and use of biological materials for research.[12] The key ethical issues addressed in this body of literature include, but are not limited to, the scope of informed consent, the content in consent documents, the nature of research risks, the confidentiality of research data, the scope of research, and the disclosure of research results. Yet to date, only a few studies have empirically examined how investigators and institutional review boards (IRBs) address these ethical issues, particularly with regard to genetic research with stored biological materials. IRB policies vary regarding the requirement for and scope of consent, the disclosure of research results, and whether researchers can contact individuals again for additional health information.[13]

For the study reported here, we examined how research conducted at several federally funded institutions designated as Clinical Research Centers (CRCs, general and pediatric) or

Specialized Programs of Research Excellence (SPOREs) addressed the issues of consent, control over biological materials, confidentiality, and disclosure of results in protocols and consent forms for genetic research with stored biological materials.

Study Methods

CRCs are federally funded centers that provide the research infrastructure—including physical space, equipment, laboratory facilities, and access to experts in critical disciplines—to conduct sophisticated, patient-oriented research. The general and pediatric CRCs differ in terms of the populations they serve.[14] SPOREs are federally funded programs designed to promote novel, interdisciplinary cancer research, with the specific goal of moving basic research findings from the laboratory to clinical settings.[15]

We sought study documents from the CRCs and SPOREs located at the medical schools and research institutions that receive the most funding from the National Institutes of Health (NIH). We chose these institutions because they conduct the most research (based on NIH funding)16 and because CRCs and SPOREs are intended to set standards for high-quality research.17 We recruited CRCs and SPOREs sequentially based on their funding ranking, starting from the institutions that received the most funding. For institutions with more than one CRC, we selected either the main campus CRC or the one with the most NIH funding. If a CRC declined to participate, did not respond, or withdrew from our study after agreeing to participate, we replaced it with the next-largest CRC at the same institution (if one existed). Because we found no readily accessible information about the relative size of SPOREs and because some institutions have several SPOREs, we randomly selected one SPORE from the institutions that had more than one. If all CRCs or SPOREs at a particular institution declined to participate, we invited the next-highest-funded institution on the NIH list.

We e-mailed the director of each CRC and SPORE, inviting his or her program to participate in our study. The documents requested for review were the eight most recent eligible protocols and corresponding consent forms (see below) from the CRCs in the sample and the two most recent eligible protocols and corresponding consent forms from the SPOREs. We requested that each participating CRC and SPORE inform their investigators about our study and ask them for permission to share the requested documents with us. We provided the CRCs and SPOREs with an information sheet detailing the procedures, risks, benefits, confidentiality protections, and compensation of the study to distribute to the investigators of protocols that were eligible for our study. Investigators responded directly to the CRC/SPORE contact person.

Documents were eligible for inclusion in the study if they indicated that 1) stored biological materials would be used for genetic (DNA) testing; 2) biological materials would be stored for future genetic (DNA) testing; or 3) biological materials would be stored for future research where future genetic (DNA) testing is neither explicitly contemplated nor prohibited. CRCs and SPOREs were given the option to screen for eligible documents themselves or to permit our research team to screen for the documents using annual reports, meeting minutes, and other resources to identify them. Final eligibility was verified upon receipt; replacement documents were requested if needed.

We allowed participating institutions to choose whether the CRC, the SPORE, or our research team would redact identifying information (e.g., name of institutions, principal investigators, other research personnel, study sponsor, and investigational drug). If our research team redacted the information, the task was completed immediately upon receipt of the documents, and the unredacted documents were then destroyed. In all cases, the research team reviewed the documents to verify complete redaction.

Anonymized documents were imported into Atlas. ti™, an electronic database for qualitative coding and analysis. Two members of the research team coded each document according to preestablished topics to ensure consistency in coding (see Table 1). The topics were selected based on our review of the literature—including existing guidelines—and input from our advisory board, which was composed of five individuals with expertise regarding research with stored biological materials and the ethical issues related to it. The team members compared coding when it was complete and resolved any disagreements through discussion among themselves. In some instances while coding the documents, the research team identified issues that raised concerns (e.g., approaches that might violate federal human research regulations or guidance or underlying ethical principles). Consensus about including these matters for analysis was achieved through consultation with the advisory board.

We conducted chi-square statistical tests adjusted for clustering by institution to determine whether and to what degree failure to discuss certain topics or practices that conflict with the federal regulations varied by investigator, protocol, or institutional characteristics. In particular, we looked at whether frequency varied by the source of the document (CRC or SPORE), study sponsor (government, industry, other), investigator training (MD, PhD) or experience (rank); whether genetics was a specific aim of the study; and whether the institution was public or private.

Study Findings

We invited 45 CRCs to participate in our study. Of these, five were ineligible because they lacked protocols meeting our criteria. We received documents from 20 of the remaining 40 CRCs. Seventeen of the participating CRCs were general CRCs, and three were pediatric ones. Of the 35 SPOREs that were invited to participate, 19 agreed to join the study. The overall response rate was 52% (39 of 75 eligible institutions).

Not every participating institution was able to provide us with the requested number of documents. We ultimately received documents for 139 studies: 115 of the studies were from CRCs, and 24 were from SPOREs. Specific characteristics of the protocols, investigators, and institutions are summarized in Table 2. We determined whether the studies mentioned our topics of analysis in the consent form, the protocol, or both. Except where noted, we report when the studies addressed the topics in at least one of the documents (consent form or protocol), with the understanding that the documents are typically treated as a set.

Storing Biological Materials

Nearly all of the studies in our sample (95%, 132 of 139) expressly stated that biological materials would be stored for future research (although, as discussed below, one of these did so only in the protocol). Four other studies implied storage in discussions regarding coding as a method of deidentifying biological materials and data, ownership of the biological materials, and future uses of them. An additional two studies did not specify whether the biological materials would be stored or destroyed after they were used for the specific study. One study used only existing biological materials and thus did not store any for future use. Fifty-four percent of studies (75 of 139) discussed how long biological materials would be stored, with 73% (55 of 75) indicating that materials would be stored indefinitely (also described in the documents as “a long time”; “many years”; or, in one case, “forever”). The remaining 27% (20 of 75) described a fixed time of retention, ranging from one to 20 years, although four of these studies used language like “at least” and “or more” that suggested biological materials might be kept longer than a specified time. Seventy-three percent of all studies (101 of 139) specifically indicated that the materials could be used for genetic or DNA research.

Consent Options

Three-quarters of the studies (104 of 139) used consent forms that offered individuals the option of designating how their biological materials could be used, including whether the materials could be stored (52.5%); whether participants could be contacted again in the future (31.7%); whether the materials could be used for genetic testing (25.2%); and whether the materials could be shared with researchers not on the original research team (16.5%). In addition, a few studies (12.9%) offered options for participants to designate how their biological materials could be used in future research—for instance, by specifying whether identifiers may be retained, or the research topics for which the materials could be used. Participants indicated their choices by marking a box (yes or no) or initialing the option either within the body of the consent form or at the end of the document.

Research Risks

Nearly all of the studies (97.8%) referred to physical risks associated with donating biological materials for storage. However, less than half (47%) discussed potential psychosocial risks, such as discrimination (29%), family discord (17%), stress (11%), stigmatization (1%), and loss of social support (1%).

Confidentiality

Nearly all of the studies (95.7%) discussed confidentiality protections related to research with biological materials. Most of the studies (78.2%) indicated that a coding scheme would be used to unlink identifiable information from the materials, but only three studies specified how the code would be assigned. One of those studies indicated that the initials of individuals' names would be linked to biological materials that were used internally. Additional steps taken to protect confidentiality included limiting access to identifying information (50.3%), publishing only unidentified information (27.3%), protecting access to sample-related computer databases (22.3%), and protecting medical records used in the study (in addition to requirements under the Privacy Rule of the Health Insurance Portability and Accountability Act [HIPAA]) (12.9%).

Twenty-nine studies (20.9%) indicated that they obtained a Certificate of Confidentiality from the NIH, which protects the investigator/institution from being compelled to disclose identifying information pursuant to a subpoena. Nineteen of these studies had genetic research as one of the primary aims, including two that involved only biobanking; the remainder were treatment protocols for HIV (seven), cancer (two), and hepatitis C (one) that also stored biological materials for future use. Similarly, 15.1% of studies indicated whether participant information may be disclosed to others not on the research team. A few studies (3.6%) indicated that information would never be disclosed to a third party, and 2.2% said participants would be contacted again for permission for such disclosure. The others said that information might be disclosed to unspecified third parties (11%), as required by law (4.3%), as part of an audit (2.1%), and to a physician (1.4%).

Research Use of Samples

Fifty-eight percent of the studies (81 of 139) indicated how materials will be used, with most of these (69.1%, 56 of 81) limiting future research use to specific conditions or uses, while the rest placed no limit on future research. However, four of the studies did not permit biological materials to be sold, and three required permission from participants to expand future use beyond the specified disease or condition in the initial study.

Sharing Stored Materials

The majority of the studies (66.9%, 93 of 139) stated that stored biological materials would be shared. About half of these (54.8%, 51 of 93) discussed with whom the materials would be shared, including researchers at other institutions (47.3%, 44 of 93), researchers at their own institution (30.1%, 28 of 93), and private, commercial entities (18.3%, 17 of 93). Of those who planned to share biological materials, 27.2% (25 of 93) described a plan for ensuring that the recipients comply with restrictions concerning use of the materials, including 12 that required IRB approval, six that required scientific approval (by the principal investigator or a formal committee), and seven that required both IRB and scientific approval. Only 2.8% of the studies (four of 139) indicated they would never share biological materials outside the specific research team. Over three-quarters of studies that discussed sharing biological materials (72 of 93) also discussed what information would be shared. Almost all of these (69 of 72) indicated that no identifying information would be shared, although three studies (from the same institution) asked participants whether they would be willing to have their materials shared with identifiers attached.

Withdrawing Stored Materials

Although all of the studies in our sample described the general right to withdraw from study participation, only 70.5% (98 of 139) described the right to withdraw stored biological materials. The majority of those permitting withdrawal of the biological materials (69.4%, 68 of 98) did so without restriction. Another 18.4% (18 of 98) noted restrictions on withdrawal when the biological materials had been deidentified (nine of 18), had already been shared (five of 18) (generally because they had been deidentified), or had already been used (four of 18), so that continued use was necessary to maintain the scientific integrity of the ongoing project. Nine studies (9.2%) indicated that materials would not be withdrawn, but that the researchers would remove identifiers from them and continue to use the deidentified materials for research. No study provided reasons for using this approach. In contrast, four studies that otherwise permitted unrestricted withdrawal asked participants whether they would agree with this approach. Three studies (3%, three of 98) indicated that materials would be withdrawn if the participant withdrew from the primary study. Twenty studies (20.4%) that discussed withdrawal of biological materials required a written request for withdrawal.

Commercial Use

Fifty-three percent of the studies (74 of 139) mentioned the issue of commercial use of individuals' biological materials, with most of these (90.5%, 67 of 74) permitting such use; only 8.1% (six of 74) prohibited the commercial use of biological materials. Almost all of the studies that permitted commercial use (65 of 67) also stated that individuals from whom the biological materials were obtained would not benefit financially from any commercialization.

Disclosing Research Results

Sixty-four percent of studies (89 of 139) discussed whether research results would be disclosed to research participants, with most of these (97.8%, 87 of 89) stating that researchers would not provide research results to study participants. Over one-third of these (35 of 89) explained why results would not be disclosed. Explanations included that the meaning of results would be unclear (22), that results would not confer a benefit (five), that the tests are experimental (three), that nondisclosure provided protection against discrimination (three), and that disclosure of individual results was impossible because the materials had been deidentified (two). Over one-quarter of the studies that discussed disclosure (23 of 89) had exceptions to the nondisclosure policy. Three studies would

provide results upon request of the participant. The remaining 20 would disclose results when disclosure could change clinical care, although four studies limited this exception to the condition being studied, and four specified that they would provide only general, not individual, results under those circumstances. One study indicated that it would provide general, not individual, results to participants because of the uncertainty of the results. Finally, one study gave participants the option of receiving general, specific, or no results, although it explained that it might take years for results to emerge and that individual results might not be available.

Pediatric Issues

None of the studies that included children mentioned plans to obtain their consent when they became legal adults or to inform them that their biological materials were being stored for use in future research. Indeed, none of these studies even raised the issue.

Practices and Regulatory Rules and Guidance

We identified some practices in approved protocols that appear not to comply with federal regulations governing research with humans or that fall outside the scope of permitted activities described in regulatory guidance documents.

First, one study protocol indicated that researchers would store study participants' biological materials and discussed the value of this collection for future research, including genetic research. However, the consent form made no mention of storage and research use. Thus, based on the consent form, individuals who consented to participate in this study would not have given consent to such uses of their biological materials and may not even have known that their biological materials would be stored for future research. Even if the information missing from the consent document had been provided orally to prospective participants during the consent process, we believe the regulations require such information to be in the written consent form.

Second, nine studies indicated that if participants requested that their biological materials be withdrawn from the study, researchers were permitted to deidentify the materials and continue to use them in research (see Table 3 for specific language). Guidance from the Office for Human Research Protections (OHRP) states that when certain conditions are met, research with biological materials that do not have identifiers does not constitute human subjects research, and thus, investigators do not need to obtain consent.[18] However, this scenario does not apply to situations in which the participant has previously given consent for research with her biological materials and then later decides to discontinue participation in research. Deidentifying her biological materials and continuing to use them, rather than destroying them, would violate her wish to no longer participate in biospecimen-related research.

Finally, although the federal regulations state that "no informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence,"[19] three studies included exculpatory language in their consent forms (see Table 3 for specific language). Interestingly, we found one example in which the protocol included exculpatory language relating to results or information generated from future research with the biological materials, but that language was not included in the consent form.

Comparison of Investigator Practices

Studies that collected biological materials for future genetic research were more likely than other studies to discuss how the materials may be used in the future ($p = 0.021$), including for genetic research ($p = 0.000$) and possibly sharing the biospecimens with other researchers ($p = 0.004$). Similarly, protocols specifically for biobanking ($p = 0.026$) and SPORE protocols ($p = 0.018$) were more likely to discuss possible sharing of biological materials than other types of protocols. Investigators who were assistant and associate professors were less likely to discuss some topics than those with a higher academic rank (see Table 4).

Discussion

We found that a majority of the documents reviewed raised most of the issues addressed in the research ethics literature. For example, almost all studies collecting biological materials prospectively informed participants that their materials might be stored and asked for permission to do so. In addition, consent was almost always sought, even for the use of existing materials, which potentially could be used without consent.[20] About three-quarters of studies indicated that biological materials might be used in genetic or DNA research and offered participants at least some options in the consent form about future use of their materials. Almost all studies discussed confidentiality protections.

On the other hand, many studies did not address topics that have been identified in the literature as important. First, over one-third of studies did not mention whether participants would receive results from future research. There may be restrictions on providing such results even if they are clinically relevant if the testing was conducted in a laboratory that does not meet federal regulatory standards.[21] However, under some circumstances, researchers may have an obligation to disclose research results.[22] Thus, participants need to be informed about whether results will be disclosed, especially since many research participants want such information.[23] Second, although all studies discussed the right to withdraw from research generally, almost 30% failed to discuss this right specifically with respect to research involving biological materials. A recent federal appeals court decision suggests this omission could limit individuals' right to withdraw their biological materials from research use.[24] Thus, specific discussion of the right to withdraw biological materials may be necessary to preserve this basic right regarding participation in research.

Finally, none of the studies involving children mentioned obtaining consent from the children when they become legal adults and thus by law are defined as capable of providing or withholding consent for research participation.[25] Moreover, these studies did not explain the reason for this omission. Children may not agree with the decisions their parents make on their behalf and may object to some research uses of their biological materials. If their materials could continue to be used into their adulthood, contacting them for consent for continued research with their materials might be the only way to fulfill the ethical principle of respect for autonomy.[26] There are certainly costs—both scientifically, in terms of biological materials that may not be used for research, and administratively, in terms of time and effort to contact the sources of the materials. And in some cases it may be legally permissible to use the materials without consent from children when they become legal adults. Nonetheless, it is striking that the issue simply was not addressed in the documents we examined.[27]

A few other topics whose importance the literature disagrees about were also not addressed in some of the studies in our sample. For example, nearly half of the studies failed to discuss the length of storage and specific coding schemes to render the materials deidentified. There is debate about how important such details are to individuals' decision-making regarding

research with biological materials.[28] Including too much detail could detract from the consent process by burdening an already lengthy process without providing corresponding benefit (e.g., improving participant understanding).[29] On the other hand, leaving out information that participants consider important may compromise the consent process.

Psychosocial risks also were rarely discussed in the documents we examined. Some commentators have argued that it may be especially important to discuss psychosocial risks associated with storage and future use of biological materials in research involving highly penetrant genes[30] (which are not the focus of typical genetic studies), since individuals with a mutation of a highly penetrant gene are at higher risk of developing the associated disease. But most genetic conditions are not caused by highly penetrant genes. On the other hand, a recent lawsuit involving the use of biospecimens reveals that some research participants may experience psychosocial harms even when the research doesn't involve highly penetrant genes.[31] Discussion of such risks may be more important when the type of future research that will be conducted is uncertain. More information is needed about how participants value different pieces of information in deciding whether to permit their DNA to be stored and used for future research to help determine the best balance between disclosing information and simplifying consent.

Not surprisingly, those studies that clearly contemplated using specimens for future genetic research were more likely to discuss some topics related to such use. Protocols that included future research as an aim, whose purpose was to bank biological materials, and protocols from SPOREs—which view banking as a core component of their research—were more likely to address the matter of sharing biological materials. However, such protocols represented a small percentage of the number of protocols we examined that collected materials for future research. If typical, greater educational efforts may be needed to prompt investigators and IRBs to consider these issues.

Some of the approaches taken in the protocols we studied may unintentionally restrict future use of biological materials. For example, there was a tendency to obtain participant consent even when regulatory exemptions regarding consent might have applied. Our study did not permit us to determine whether investigators preferred to obtain consent even when federal regulatory exceptions were relevant or whether IRBs required consent as a condition of study approval. Specifying the type of research for which their biological materials may be used or offering participants options for specifying permitted uses might also restrict future research. A study of IRB chairs suggests that IRBs may be reluctant to permit research with biological materials unless consent for specific research uses is obtained.[32] Further research is warranted to determine why investigators and IRBs do not use the regulatory exemptions that might apply to research with stored biological materials.

We found only a few practices among the protocols we studied that appeared to violate federal regulations governing research with humans. One instance involved the failure to obtain consent for storing materials for future use despite an explicit intention to do so. Other studies (2%) used language designed to have participants waive legal rights, in express violation of the regulatory prohibition regarding the use of exculpatory language. Because all studies had to have IRB and CRC or SPORE approval to be eligible for our study, finding any such practices is troubling. These findings, coupled with our findings about omitted topics, suggest that further education of investigators and IRB members is needed on these topics.

Although we examined what information was contained in and omitted from consent forms, we recognize the limits of written consent forms as a proxy for the information provided to prospective participants in the consent process. Some information may be relevant to the

consent and conduct of the study or to the oversight process, but does not need to be in the consent form. However, we found that some details—such as procedures for coding information to render it unidentifiable—were often missing from both the consent form and the protocol. This lack of detail is a matter for concern for at least two reasons. First, IRBs may not have the details they need to evaluate whether coding procedures will adequately deidentify the biological materials. Second, without explicit procedures for coding biological materials, investigators may omit steps that are necessary to protect the confidentiality of research data. It is possible that these details may be in other materials (e.g., in an operations manual) that we did not receive. Nevertheless, it is important that these details be described to, and assessed by, the IRB, even if they are not included in the consent form.

Other limitations of our study should be kept in mind. Our analysis is based on information contained in protocols and consent forms. These documents told us what the researchers proposed to do, but they did not tell us what researchers actually did in practice. In addition, we did not look at other documents—such as IRB minutes or institutional guidance materials and templates—that might provide information about how the researchers' plan was shaped by other factors or whether institutions followed their own policies and recommendations. Nor did we collect study documents submitted over the life of the studies to determine whether changes were made to the protocols or consent forms.

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The IRBs at the University of California, San Francisco (Committee on Human Research), and Georgia State University approved this study. The study was designed to be exempt from federal regulatory requirements. It was also designed so that respondents would not be considered researchers "engaged in research" under the regulations. However, because IRBs may interpret the regulations differently, we encouraged CRCs and SPOREs to check with their local IRBs about their requirements and provided assistance. Where required, local IRB approval was obtained.

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Table 1

Coding Topics

Major Topics	Research Questions
Consent	Is consent (permission/assent in pediatric studies) to use biological materials for genetic research sought?
	If consent is not sought, what justification is provided in protocol?
	If consent is sought, what is the consent process?
	For pediatric research, is consent sought from a child who reaches majority?
Control and use of biological materials	Is the length of storage specified?
	Does the donor have any control over his or her biological materials?
	Can the biological materials be shared with other researchers?
	Are commercial uses of the biological materials permitted?
Confidentiality	Are steps that will be taken to protect the confidentiality of participant information discussed (e.g., coding, limiting access to information, Certificate of Confidentiality)?
	Under what circumstances will information be disclosed to third parties (e.g., audits, reportable conditions, other legal requirements, threat to identified third parties, others)?
Disclosing research results to donors	Will research participants receive results of genetic testing or other research results?
	If so, under what circumstances?
	For pediatric populations: If information will be disclosed, with whom will the information be shared (the parents, the child, or both)?

Table 2

Sample Characteristics

	All Institutions	GCRCs	SPOREs
Protocol Characteristics	**n = 139**	**n = 115**	**n = 24**
Sponsor			
Government	104 (74.8%)	86 (74.8%)	18 (75%)
Industry	18 (13.0%)	17 (14.8%)	1 (4.2%)
Other	5 (3.6%)	3 (2.6%)	2 (8.3%)
Missing	12 (8.6%)	9 (7.8%)	3 (12.5%)
Study type			
Nontreatment	67 (48.2%)	64 (55.7%)	3 (12.5%)
Tissue procurement/banking only	25 (18.0%)	6 (5.2%)	19 (79.2%)
Treatment	46 (33.1%)	45 (39.1%)	1 (4.2%)
Other	1 (0.7%)	0 (0.0%)	1 (4.2%)
Human biological materials collection			
Prospective	127 (91.4%)	112 (97.4%)	15 (62.5%)
Existing	7 (5.0%)	2 (1.7%)	5 (20.1%)
Mixed	5 (3.6%)	1 (0.9%)	4 (16.7%)
Genetics			
Primary aim	46 (33.1%)	43 (37.4%)	3 (12.5%)
Secondary aim	45 (32.3%)	43 (37.4%)	2 (8.3%)
Future research	23 (16.6%)	12 (10.4%)	11 (45.8%)
Not mentioned in protocol/consent	25 (18.0%)	17 (14.8%)	8 (33.3%)
Age			
Adult	89 (64.0%)	71 (61.7%)	18 (75%)
Child	15 (10.8%)	15 (13.0%)	0 (0.0%)
Adult, child	33 (23.7%)	29 (25.2%)	4 (16.7%)
Not available in data	2 (1.4%)	0 (0.0%)	2 (8.3%)
Investigator Characteristics	*n = 130*	*n = 106*	*n = 24*
Degree			
MD	83 (63.8%)	74 (69.8%)	9 (35.7%)
MD+	24 (18.5%)	17 (16.0%)	7 (29.2%)
PhD	18 (13.9%)	11 (10.4%)	7 (29.2%)
PhD+	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	3 (2.3%)	2 (1.9%)	1 (4.2%)
Missing	2 (1.5%)	2 (1.9%)	0 (0.0%)
Rank			
Professor	64 (49.2%)	49 (46.2%)	15 (62.5%)
Associate professor	26 (20.0%)	22 (20.8%)	4 (16.7%)
Assistant professor	26 (20.0%)	24 (22.6%)	2 (8.3%)
Other	5 (3.9%)	3 (2.8%)	2 (8.3%)
Missing	9 (6.9%)	8 (7.6%)	1 (4.2%)

	All Institutions	GCRCs	SPOREs
Protocol Characteristics	**n = 139**	**n = 115**	**n = 24**
Institutional Characteristics	*n = 36*	*n = 17*	*n = 19*
Public	18 (50%)	10 (58.9%)	8 (42.1%)
Private	18 (50%)	7 (41.1%)	11 (57.9%)
Geographic location	—	—	—
Northeast	8 (22.2%)	4 (23.5%)	4 (21.1%)
Southeast	8 (22.2%)	2 (11.8%)	6 (31.6%)
Midwest/central	9 (25%)	5 (29.4%)	4 (21.1%)
West	11 (30.6%)	6 (35.3%)	5 (26.3%)

Table 3

Text of Problematic Language

Topic	Problematic Language
Withdrawal	*Example 1:* If you withdraw any tissue or blood samples that were collected from you, they either will be destroyed or stored without any information that identifies you. *Example 2:* For withdrawal of samples: If you agree to allow your tissue/blood/cells to be kept for research, you are free to change your mind at any time. We ask that you contact [researcher name] in writing and let him know you are withdrawing your permission for your blood to be used for research…. Any unused blood will have all identifying information removed that would link the sample to you. The sample may then be used for other research, but no one will be able to relate those research results to you. *Example 3:* If in the future you decide you no longer want to participate in this research, we will remove your name and any other identifiers from your blood samples/genetic information, but the material will not be destroyed, and we will continue to use it for research.
Exculpatory language	*Example 4:* By agreeing to allow your samples to be stored and used in future research, *you agree to give up all ownership and rights to the samples*, and to DNA/cells extracted from those samples, including any potential profit from commercial development from your samples. Your DNA/cells become the property of [the institution]. *(emphasis added)* *Example 5:* By agreeing to participate in this study, *you agree to waive any claim* that you might have to the body tissues and fluids that you donate. It is possible that samples you have donated, which are used in research, may result in new products, tests, or discoveries. In some instances, these may have value and may be developed and owned by the study sponsor or others. Participation in this research means that you waive the right to any new material or process developed through this research. *(emphasis added)* *Example 6:* This is being done for our research purposes only. Researchers would like to know about your family's history of diabetes and other diseases. You will not learn anything through this research about yourself or your family members and, should you participate in this study, *you agree to waive access* to or review of your information related to the study indefinitely. *(emphasis added)*

Table 4

Outcomes

	Type of Genetic Aims in Underlying Study				
Percentage failing to discuss:	**Primary (n = 47)**	**Secondary (n = 43)**	**Future (n = 23)**	**None specified (n = 24)**	**P-value[1]**
Sharing of specimens	25.5%	46.5%	4.3%	37.5%	0.004
Potential future uses of specimens	48.9%	48.8%	17.4%	50.0%	0.021
That future research may include genetic research	12.8%	20.9%	4.3%	87.5%	0.000
	Investigator Rank				
	Assistant professor (n = 27)	Associate professor (n = 29)	Professor (n = 69)	Other (n = 4)	
Sharing of specimens	44.4%	51.7%	34.8%	0.0%	0.008
Potential future uses of specimens	59.36%	41.38%	36.23%	75%	0.051
	Study Sponsor				
	Government (n = 104)	Industry (n = 7)	Other (n = 3)		
That future research may include genetic research	23.1%	41.2%	50.0%		0.013
	Type of Protocol				
	Banking (n = 18)	Investigator (n = 121)			
Sharing of specimens	5.6%	33.9%			0.026
	Source of Documents				
	GCRC (n = 75)	SPOREs (n = 22)			
Sharing of specimens	53.3%	9.1%			0.018

[1] Chi-square test adjusted for clustering by institution.