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Genetic Research Involving Human Biological Materials:

A Need to Tailor Consent Forms

BY SARA CHANDROS HULL, HOLLY GOODING, ALISON P. KLEIN, ESTHER WARSHAUER-BAKER, SUSAN METOSKY, AND BENJAMIN S. WILFOND

There has been expanding interest in genetic research in recent years, including the use of human biological materials, with a corresponding surge of attention to informed consent for such research. Although the regulations governing the conduct of federally-funded research involving human subjects (the "Common Rule") provide guidance on the general content of informed consent, they do not address concerns that are specific to genetic research, including research on human biological materials. Several recent position papers have provided more specific guidance on the consent process for genetic research,[1] and several groups have developed model consent form templates for prospective sample collection.[2] Most call for specific disclosure of the risks associated with genetic research, particularly those associated with release (both inadvertent and deliberate) of personal genetic information. The release of genetic information could have negative consequences causing individuals to be anxious about their health, complicating their interactions with family members or causing economic ramifications if revealed to third parties such as employers or insurance companies.[3]

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There is some disagreement about approaches to consent for collection and use of human biological materials. For example, some recommend that details about potential secondary uses of samples for research be provided to subjects including the type of diseases to be studied, whether additional consent will be sought in certain circumstances, and whether samples will be identified, coded, or anonymous.[4] However, others believe this level of detail to be burdensome for both the research subject and the researcher, and instead recommend that subjects be asked simply to consent broadly to donation of their samples for any secondary research and educational purposes.[5] A third alternative is for researchers to recontact subjects prior to any secondary research use of their samples to obtain consent based on the specific details of each new project.[6] What these recommendations have in common is their lack of distinction between varying study purposes and risk levles of research involving human biological materials.

Few data are available that examine the impact of recent guidelines on the informed consent process for genetic research. One study that evaluated the content of 103 consent forms for genetic research[7] pre-dated recent policy statements that offered guidance on drafting such consent forms and

therefore does not reflect their potential influence on consent form content. A recent study found variations in how thirty-one different Institutional Review Boards (IRBs) reviewed a single, multicenter genetic epidemiology trial,[8] affirming a previously documented trend of significant IRB variation in review of single multicenter trials.[9] IRBs have also been found to vary in their informed consent requirements across different studies involving stored biological samples; this variation was related to the IRBs' use of prominent guidance documents as well as the volume of protocols reviewed annually.[10]

The purpose of our study was to conduct a comprehensive content analysis of all available consent forms within a particular setting to determine what information currently is being provided to research subjects concerning the use of their biological materials for genetic research.

Table 1: NIH Clinical Center Studies that Describe "Genetics/Secondary Research"

NIH IRBs	*(N)*
National Cancer Institute	67
National Heart, Lung, and Blood Institute	46
National Institute of Allergy and Infectious Diseases	39
National Institute of Child Health and Human Development	25
National Institute of Diabetes and Digestive and Kidney Diseases	24
National Institute of Mental Health	16
National Human Genome Research Institute	14
National Institute of Neurological Disorders and Stroke	14
National Institute of Dental and Craniofacial Research	6
National Eye Institute	5
National Institute on Aging	1
National Institute on Alcohol Abuse and Alcoholism	1
Total	**258**

Methods

Site and Sample. In August 2000, 832 active intramural National Institutes of Health (NIH) studies with consent forms were identified from an Intranet website maintained by the Warren G. Magnuson Clinical Center. These consent forms correspond to research that is reviewed by one of fourteen NIH IRBs, each of which functions independently within this research hospital setting under the oversight of a single Office for Human Subjects Research. The consent forms were reviewed in their entirety to determine which contained language about the use of human biological materials for genetic research and/or storage of biological materials for secondary research beyond the current stated research objectives ("genetics/secondary use"). Of the 832 studies identified, 258 had consent forms that included such language. A single consent form was selected from each of these 258 studies for our evaluation. For studies with two or more consent forms (e.g., for multiple study populations or purposes), the consent form containing the greatest amount of information about planned collection, use, and/or storage of human biological materials for genetic research was selected.

Table 2: Types of Studies Represented in Consent Forms

	Participant Involvement		
	Individuals Only	*Multiple Family Members*	*Total*
	No. (%)	*No. (%)*	*No. (%)*
Genetics/Secondary Research as "Major" Purpose	66 (39%)	73 (84%)	139 (54%)
Genetics/Secondary Research as "Minor" Purpose	105 (61%)	14 (16%)	119 (46%)
Total	**171**	**87**	**258**

Data Collection and Analysis

A coding form was developed based on a review of policy recommendations regarding the content and format of consent forms for genetic research involving human tissue samples. The coding form was revised based on a pilot analysis of fifty consent forms. For each consent form, information was recorded about whether genetics/secondary research was a "major" or "minor" focus of the study. Genetics/secondary research was considered a "major" study purpose if it was a primary aim of the study, i.e., mentioned within the title of the study or the first paragraph of the consent form. Up to two major and minor purposes were recorded for each consent form. In addition, the inclusion or absence of information about the following six broad content domains was recorded: (1) pro-

Table 3: Inclusion of Consent Form Domains

Domain Mentioned	*Total (N=258)*	*Individual Major (N=66)*	*Individual Minor (N=105)*	*Family Major (N=73)*	*Family Minor (N=14)*
Providing genetic results					
Yes	173 (67%)	51 (77%)	44 (42%)	69 (95%)	9 (64%)
No	85 (33%)	15 (23%)	61 (58%)	4 (5%)	5 (35)
OR (95%CI)	--	Ref	*0.21 (0.11-0.43)	*5.07 (1.59-16.20)	0.53 (0.15-1.82)
Genetic-specific risks					
Yes	161 (62%)	42 (64%)	43 (41%)	68 (93%)	8 (57%)
No	97 (38%)	24 (36%)	62 (59%)	5 (7%)	6 (43%)
OR (95%CI)	--	Ref	*0.40 (0.21-0.75)	*7.77 (2.74-21.931)	0.76 (0.24-2.46)
Confidentiality					
Yes	178 (69%)	49 (74%)	60 (57%)	62 (85%)	7 (50%)
No	80 (31%)	17 (26%)	45 (43%)	11 (15%)	7 (50%)
OR (95%CI)	--	Ref	*0.46 (0.24-0.91)	1.96 (0.84-4.56)	0.35 (0.11-1.13)
Ownership					
Yes	41 (16%)	9 (14%)	13 (12%)	17 (23%)	2 (12%)
No	217 (84%)	57 (86%)	92 (88%)	56 (77%)	12 (86%)
OR (95%CI)	--	Ref	0.90 (0.36-2.23)	1.92 (0.79-4.67)	1.06 (0.20-5.52)
Sample storage					
Yes	188 (73%)	43 (65%)	74 (70%)	60 (82%)	11 (79%)
No	70 (27%)	23 (35%)	31 (30%)	13 (18%)	3 (21%)
OR (95%CI)	--	Ref	1.28 (0.66-2.46)	*2.47 (1.13-5.41)	1.96 (0.50-7.74)
Withdrawal					
Yes	71 (28%)	10 (15%)	15 (14%)	41 (56%)	5 (36%)
No	187 (72%)	56 (85%)	90 (86%)	32 (44%)	9 (64%)
OR (95%CI)	--	Ref	0.93 (0.39-2.22)	*7.18 (3.17-16.23)	3.11 (0.86-11.23)

*p< .05

viding genetic results to subjects; (2) genetic-specific risks; (3) confidentiality protections; (4) ownership/commercial use of samples; (5) sample storage; and (6) withdrawal (i.e., what happens to samples and data when a subject withdraws from the study).

Finally, the coding form characterized the description of plans to conduct secondary research in the future using stored biological materials collected from research subjects. Coders assessed the inclusion of the various content areas without making judgments about the quality or appropriateness of the language. Coders did not code the "boilerplate" statements that are required in all NIH intramural consent forms, which include general language about a subject's ability to withdraw from the study and confidentiality protections for NIH research records.

Each consent form was coded independently by two coders who then met to reconcile discrepancies. There were discrepancies that required reconciling in approximately 7% of all items coded after the pilot phase. A reconciled coding form representing the coders' consensus for each consent form was entered into SAS statistical software for analysis. Frequencies were generated for all coding form items, and logistical regression was used to determine the relationship of the study type to the inclusion of content domains. This study did not examine differences between individual IRBs, as this was not one of our aims. To conduct a meaningful analysis of IRB variation would have required corroboration of our data with guidance documents and templates from each of the IRB's; this was beyond the scope of this study.

Results

Characteristics of Consent Forms. The 258 consent forms were reviewed and approved by one of 12 out of the 14 NIH IRBs (Table 1). These 258 consent forms included 171 (66%) studies involving the collection of biological materials only from individuals, and 87 studies (34%) involving multiple family members (Table 2). Genetics/secondary research was a *major* purpose of the study in 139 (54%) of these consent forms, while it was a *minor*

purpose of the study in 119 (46%) consent forms. Additional study purposes included natural history or physiologic monitoring (123; 48%), drug intervention or treatment (89; 34%), and collection of tissues for immediate therapeutic use such as for bone marrow transplantation (15; 6%).

Current Genetic Research

Of the six content domains, providing genetic results, genetic-specific risks, confidentiality protections, and sample storage were mentioned in a majority of the consent forms (62%-73%). However, ownership/commercial use of samples (16%) and withdrawal (28%) were rarely mentioned (Table 3). Seventeen (7%) forms did not mention of any of the six domains. Studies involving multiple family members in which genetics was a major purpose ("family major" studies) were significantly more likely to include the domains of providing genetic results, genetic-specific risks, sample storage, and withdrawal as compared to "individual major" studies. In contrast, "individual minor" studies were less likely to address the domains of providing genetic results, risk, and confidentiality as compared to "individual major" studies.

A typical "individual minor" consent form for early phase cancer vaccine research included detailed risk information about the potential side effects of the components of the vaccine, yet provided no information about the potential risks associated with the planned research on subjects' blood. The consent form stated simply that "the results of research on your blood cells may help find new ways to learn about, prevent, or treat cancer and other diseases."

The inclusion of specific topics within each of the six content domains is summarized in Table 4. Fewer than half of all consent forms mentioned any particular topic; the most commonly mentioned topics included the risks of potential discrimination (48%), whether anticipated study results might be shared with study participants (46%), and whether unanticipated study results might be shared with study participants (42%). Of the 145 studies that stated affirmatively that results would or might be shared with participants, 129 (89%) included at least some amount of information on genetic-specific risks. Of the 87 consent forms for studies involving multiple family members, 61 (80%) discussed the risks of learning about misattributed paternity. Inappropriately, 38 (22%) of the 171 consent forms for studies that clearly do not involve family members also included language about misattributed paternity, although such language would not be relevant to non-family studies.

While confidentiality was addressed in a majority of the consent forms (69%), at times the language used was inconsistent. For example, 26 (10%) of the forms offered a guarantee of absolute confidentiality, even though this contradicts the NIH "boilerplate" statement about limits of confidentiality that appears on all NIH consent forms.

Table 4:
Inclusion of Specific Topics in Consent Form Content Domains

Domain	*Total (% of 258)*
Providing genetic results (n=173)	
Expected results	119 (46%)
Unanticipated results	109 (42%)
Misattributed paternity results	93 (36%)
Genetic-Specific Risks (n=161)	
Discrimination	123 (48%)
Learning about misattributed paternity or adoption	99 (38%)
Revealing familial health information	67 (26%)
Ambiguity of research results	60 (22%)
Upsetting nature of information	55 (21%)
Confidentiality Protections (n=178)	
Use of codes	79 (31%)
Removal of identifiers	40 (16%)
Certificate of Confidentiality	9 (3%)
Ownership/Commercial Use (n=41)	
Ownership	21 (8%)
Commercial Use	21 (8%)
Sample Storage (n=188)	
Method	74 (29%)
Location	47 (18%)
Length	28 (11%)
Withdrawal (n=71)	
What happens to samples	62 (24%)
What happens to data	34 (13%)

Secondary Research

There were 230 forms that described the possibility that secondary research would be conducted on samples collected in an initial study that described potential secondary research on related diseases (158; 69%), unrelated diseases (46; 20%), or general (unspecified) research (106; 46%) (Table 5). These were not mutually exclusive categories; a single consent form might articulate different conditions under which related and unrelated diseases would be studied in the future. In addition, 105 (46%) forms mentioned how confidentiality would be protected in secondary research, and 76 (33%) mentioned whether samples would be shared with other researchers.

The possibility that additional consent would be sought from research subjects before secondary research is conducted was mentioned in 97 (42%) consent forms describing such research. However, the circumstances were often contingent, depending on five conditions: whether the research would be conducted on the same or different diseases than covered in the original study (35;15%); whether the research posed any additional risks to the subjects not addressed in the current consent form (28;12%); whether samples would be used in a coded or anonymous fashion (8;4%); and whether samples would be shared with other researchers (3;1%). In addition, 34 (15%) of these consent forms stated that additional consent would be sought before any secondary research was conducted. These circumstances were not presented in a mutually exclusive manner; eleven different combinations of the five categories were found.

A minority of consent forms describing potential secondary research allowed subjects to specify up to five conditions under which their samples could be used for such research (45; 20%): when they were given the opportunity to permit or refuse secondary research of any kind (37; 16%); on unrelated diseases (16; 7%); on identifiable samples (8; 4%); by other researchers (2; 1%); or only after subjects were recontacted for additional consent (24; 10%). These options were not mutually exclusive; nine different combinations of the five option categories were found.

Discussion

The consent forms we evaluated are characterized by examples of critical omissions, unnecessary inclusions, and random variability. These characteristics suggest that investigators and/or IRBs are not approaching consent forms for genetic research using biological samples in a consistent deliberative manner. Tailoring consent forms to those genetic-related issues that are important to a subject's decisionmaking about participation in a particular study may improve their usefulness as decisionmaking tools.

There is at least a minimum amount of genetic-specific information that should be included in any consent form for genetic research. Indeed, 95% of "family major" consent forms did mention whether results would be provided to subjects, and 93% mentioned risks specific to genetic research. However, only 42% of the most common type of consent forms (for "individual minor" studies) mentioned provision of results, and only 41% mentioned any genetic-specific risks. The observation that consent forms are less likely to address key issues for studies in which genetics is a minor aspect suggests that IRBs may lose sight of these issues when other risks are present. Although it is quite appropriate for consent forms to center on the potentially serious physical risks associated with vaccine or drug trials, a comparatively brief acknowledgment of the potential risks associated with genetic research on blood samples collected as a minor purpose of such studies may also be useful to subjects. The amount of information included in consent forms about use of samples for genetic research should correspond to the specific research plans. When results will be provided to subjects, the consent form should

Table 5:
Consent Forms Describing Conditions for Conducting Secondary Research

	Total (% of 230)
Focus of research*	
Related diseases	158 (69%)
Unrelated diseases	46 (20%)
General or unspecified	106 (46%)
Confidentiality of samples*	
Identified (e.g., with names, social security #)	7 (3%)
Coded/Identifiable	89 (39%)
Unidentifiable	40 (16%)
No mention	125 (54%)
Whether samples will be shared with other researchers	
Yes, confidentiality mentioned	54 (23%)
Yes, confidentiality not mentioned	22 (10%)
No mention	154 (67%)

* The conditions within these categories were not mutually exclusive.

describe any relevant associated risks, which might include discrimination, stigmatization, anxiety, and implications for family members, depending on the nature of the test and the subjects' circumstances. However, when study results are not provided to research subjects, these risks are less likely to occur, and less information needs to be included in the consent form.

While these omissions are striking, the inclusion of inappropriate or potentially irrelevant information in consent forms is also of concern. For example, 38 (22%) consent forms for studies involving only individuals (and not their family members) included irrelevant language about the risk of learning about misattributed paternity and adoptive relationships. In addition, 26 (10%) consent forms offered a guarantee of absolute confidentiality without appropriate qualifiers. Such language reflects a mechanical (and perhaps literal) application of recommendations on what should be included in consent forms for genetic studies without attention to the particulars and realities of the research.

We observed considerable variability in consent form content regarding the conditions under which secondary research might be conducted. Specifically, five different criteria were mentioned in eleven different combinations regarding when it is appropriate to obtain additional consent for future research studies. Similarly, while options allowing subjects to make choices about secondary research were included in only 45 consent forms, there were five different options mentioned in nine different combinations. The presence of so many combinations suggests that no single or consistent rationale is being used to decide which conditions and options to include in consent forms. In the broader context of decisions that potential participants may need to make about research, such as the physical risks of investigational drugs, it is not clear that much time should be focused on considering "options" about use of data and samples. It may sometimes be sufficient simply to state that data and samples will be stored for a limited time (or indefinitely) and used for related research, or in some cases, for more general research.

This study has a number of limitations. First, the consent forms evaluated were limited to a single research institution with multiple IRBs that are coordinated by a single office. However, given the diversity of the content of consent forms that we observed even within this setting, it is likely that at least as much variability would be apparent across other research contexts. In addition, this study of consent forms provides limited insight into the consent process, which optimally occurs over time and includes a discussion between the potential subject and members of the research team.

IRBs are faced with the challenge of ensuring that consent forms include the information that will be most relevant to an individual's decision to participate in each given study, without extraneous details and meaningless choices. Guidance that recommends model consent form templates and "boilerplate" language, while seeming to standardize the process, may actually hinder the development of consent forms that are appropriately responsive to different kinds of study features. Ultimately, if the purpose of the consent process is to provide potential subjects with the information they need to make a decision about participation, the process needs to be tailored to their specific informational needs. Our data point to an important need for empirical research to determine what most subjects want to know regarding the use, storage, and future uses of their samples. Such data are essential in order to prioritize the information that is most likely to be important to effectively communicate to potential subjects of genetic research.

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■ **Sara Chandros Hull, PhD** is Head of the Research Ethics Section, Social and Behavioral Research Branch, National Human Genome Research Institute, NIH; **Holly Gooding** is currently a medical student at the University of California San Francisco; **Alison P. Klein, PhD, MHS** is a Research Fellow in the Statistical Genetics Section of the Inherited Disease Research Branch, NHGRI, NIH; **Esther Warshauer-Baker** is a postbaccalaureate fellow in the Social and Behavioral Research Branch, NHGRI, NIH; **Susan Metosky, MPH** is the Research Compliance Coordinator at Old Dominion University; and **Benjamin S. Wilfond, MD** is Head of the Bioethics and Social Policy Section, Social and Behavioral Research Branch, NHGRI, NIH.

References

1. Clayton E, Steinberg K, Khoury M, Thomson E, Andrews L, Kahn MJE, Kopelman LM, Weiss JO. Informed consent for genetic research on stored tissue samples. *JAMA* 1995;274:1786-1792; National Bioethics Advisory Commission. *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*. National Bioethics Advisory Commission: Rockville, MD, 1999; Phillips J, Cohen M, Fleisher L, Austin S, Smith A, Clayton E. ACMG Statement on storage and use of genetic materials. *American Journal of Human Genetics* 1995;57:1499-1500; American Society of Human Genetics. ASHG Report: Statement on informed consent for genetic research. *American Journal of Human Genetics* 1996;59:471-474.

2. Merz J, Sankar P. DNA banking: An empirical study of a proposed consent form.

In *Stored Tissue* Samples: Ethical, Legal, and Public Policy Implications. Iowa City: University of Iowa Press, 1998, p. 198-225; Beskow L, Burke W, Merz J, Barr PA, Terry S, Penchaszadeh VB, Gostin LO, Gwinn M, Khoury MJ. Informed consent for population-based research involving genetics. *JAMA* 2001;286:2315-2321.

3. Andrews L, Fullarton J, Holtzman N, Motulsky A. *Assessing Genetic Risks: Implications for Health and Social Policy.* Washington, DC, 1994.

4. See ref. 1, Clayton et al., 1995.

5. Grizzle W, Grody W, Noll W, Sobel ME, Stass SA, Trainer T, Traver SH, Weedh V, Woodruff K. Members of the Ad Hoc Committee on Stored Tissue, CAP. Recommended policies for uses of human tissue in research, education, and quality control. *Archives of Pathology Laboratory Medicine* 1999;123:296-300.

6. See ref. 1, National Bioethics Advisory Commission 1999.

7. Weir R, Horton J. DNA banking and informed consent, part II. *IRB: A Review of Human Subjects Research* 1995;17:1-8.

8. McWilliams R, Hoover-Fong J, Hamosh A, Beck S, Beaty T, Cutting G. Problematic variation in local institutional review of a multicenter genetic epidemiology study. *JAMA* 2003;290(3):360-366.

9. Stair T, Reed C, Radeos M, Koski G, Camargo C. Variation in institutional review board responses to a standard protocol for a multicenter trial. *Academic Emergency Medicine,* 2001;8:636-641; Silverman H, Hull SC, Sugarman J. Variability among institutional review boards' decisions within the context of a multicenter trial. *Critical Care Medicine* 2001;29:235-241.

10. White M, Gamm J. Informed consent for research on stored blood and tissue samples: A survey of institutional review board practices. *Accountability in Research* 2002;9:1-16.

ANNOTATIONS

Kim SYH, Millard W, Nisbet P, Cox C, Caine ED. Potential research participants' views regarding researcher and institutional financial conflicts of interest. *Journal of Medical Ethics* 2004;30:73-79. • The authors conducted an Internet survey with individuals diagnosed with a major chronic illness who indicated they were willing to participate in a clinical trial for a new treatment for their illness. The purpose of the survey was to ascertain respondents' views on investigator or institutional financial conflicts of interest in clinical research. Potential research participants were presented with seven scenarios involving commercial funding; personal income; per capita payments; researcher patent; university patent; researcher stocks; and university stocks. Respondents indicated that they want to be informed of financial conflicts, that disclosure should be required, and that they would participate in studies when conflicts of interest are disclosed.

Kodish E, Eder M, Noll R, Ruccione K, et al. Communication of randomization in childhood leukemia trials *JAMA* 2004;294(4):470-475. • The authors observed and audio taped informed consent conferences health care teams held with parents of children newly diagnosed with acute leukemia that were being recruited to participate in randomized clinical trials. They also interviewed parents shortly after the informed consent conference to ascertain parental understanding of the process of randomization. During the informed consent conference, physicians used various metaphors to describe randomization, the most common being the metaphors of the "coin toss" and "chance." In 17% of the informed consent conferences, physicians did not provide an explanation of randomization. Of the parents interviewed, 50% did not understand randomization. Factors associated with not understanding randomization include whether parents read the consent document, whether physicians explained randomization in the informed consent process, whether parents were from a racial or ethnic minority group, and whether parents were from a lower socio-economic background. The authors suggest 11 steps to take to improve communication of randomization in the informed consent process.

Wendler D, Shah S. Should children decide whether they are enrolled in nonbeneficial research? *American Journal of Bioethics* 2003; 3(4): 1-7. • Federal regulations governing research with children require parental permission for their child's participation and the child's assent. Yet the regulations do not specify when children are capable of giving assent. The authors contend that in the context of nonbeneficial research, the threshold for assent should be the age of 14 and that researchers should be required to respect the dissent of all children. Their position on the assent requirement stems from the principle of respect for subject autonomy and on evidence from developmental psychology that by 14 years of age children are capable of understanding the moral importance of helping others and of making their own research decisions. The authors defend the dissent requirement on the grounds that the principle of nonmaleficence requires that children should not be required to participate in nonbeneficial research that is more than minimally distressing.