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Cover Page Footnote

Support for this study was provided by a grant from the Annenberg Public Policy Center to the Center for Bioethics at the University of Pennsylvania. Thanks are extended to Peter Watson and the NCI Canada and Health Canada for support

Psychosocial Risks of Storing and Using Human Tissues in Research*

Jon F. Merz**

Introduction

Human tissues are collected and stored for numerous reasons. Many states have created forensic DNA banks;¹ the U.S. military is banking blood from soldiers with the intent to retain the samples for 50 years,² states are storing Guthrie cards from newborns,³ and other banks of newborn cord blood, tumor and normal tissues are being created.⁴ In addition, clinicians collect blood and other tissues and samples for diagnostic tests, and pathologists are required by law and good medical practices to retain tissues for many years (some archives are more than a century old).

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¹ Jean E. McEwen, *Forensic DNA Data Banking by State Crime Laboratories*, 56 *Am. J. Hum. Genet.* 1487 (1995).

² *Mayfield v. Dalton*, 901 F. Supp. 300 (D. Hawaii 1995).

³ Jean E. McEwen & Phillip R. Reilly, *Stored Guthrie Cards as DNA "Banks"*, 55 *Am. J. Hum. Genet.* 196 (1994).

⁴ See e.g., Eliot Marshall, *Clinical Promise, Ethical Quandary*, 271 *Science* 586 (1996); Jeremy Sugarman, Emily G. Reisner, Joanne Kurtzberg, *Ethical Aspects of Banking Placental Blood for Bone Marrow Transplantation*, 274 *J.A.M.A.* 1783 (1995); Bartha M. Knoppers, Claude M. Laberge, *Research and Stored Tissues: Persons as Sources, Samples as Persons?* 274 *J.A.M.A.* 1806 (1995).

Researchers also collect samples from subjects for a broad range of studies. In many of these cases, the disposition of excess tissues has not been a concern. However, with the rapid development of genetic technologies has come the ability to study stored samples and generate information about diseases and susceptibility to disease. Such information can have profound effects on the lives of people if irresponsibly handled or disclosed.

Because of the risks of misuse of such information, there have been numerous calls for constraints on the banking and use of stored tissues,⁵ as well as proposals demanding detailed informed consent for research uses of both stored and prospectively collected tissues.⁶ As two leading commentators noted before genetic technologies brought renewed focus on these issues, full disclosure or "extended informed consent" should be secured when information developed in proposed research with tissues might be linked to the source's identity and when the research might yield information having diagnostic significance that could cause stigmatization or discrimination.⁷ Yet,

⁵ See e.g., George J. Annas, *Privacy Rules for DNA Databanks: Protecting Coded 'Future Diaries'*, 270 J.A.M.A. 2346 (1993); George J. Annas, Leonard H. Glantz, Patricia A. Roche, *The Genetic Privacy Act and Commentary* (1995) (visited July 1997) <<http://www-busph.bu.edu/Depts/LW/DOCUM.HTM>>; Ellen Wright Clayton, Karen K. Steinberg, Muin J. Khoury, Elizabeth Thomson, Lori Andrews, Mary Jo Ellis Kahn, Loretta M. Kopelman, Joan O. Weiss, *Informed Consent for Genetic Research on Stored Tissue Samples*, 274 J.A.M.A. 1786 (1995).

⁶ See e.g., Clayton et al., *supra* note 5; *American College of Medical Genetics Storage of Genetics Materials Committee, Statement on Storage and Use of Genetic Materials*, 59 Am. J. Hum. Genet. 471 (1996); Robert F. Weir & Jay R. Horton, *DNA Banking and Informed Consent—Part 1*, 17(4) IRB: Rev. Human Subjects Res. 1 (1995); Robert F. Weir & Jay R. Horton, *DNA Banking and Informed Consent—Part 2*, 17(5) IRB: Rev. Human Subjects Res. 1 (1995); David E. Goldgar & Philip R. Reilly, *A Common BRCA1 Mutation in the Ashkenazim*, 11 Nature Gen. 113 (1995).

⁷ See e.g., Angela R. Holder & Robert J. Levine, *Informed Consent for Research on Specimens Obtained at Autopsy or Surgery: A Case Study in the Overprotection of Human Subjects*, 24 Clin. Res. 68 (1976). Genetic information is used for risk stratification by insurers, and there are legitimate concerns that molecular genetics will only exacerbate problems of access by those who need health insurance. Ehsan Masood, Sally Lehrman, Quirin Schiermeier, Declan Butler, Richard Nathan, *Gene Tests: Who Benefits from Risk?* 379 Nature 389 (1996); Kathy L. Hudson, Karen H. Rothenberg, Lori B. Andrews, Mary Jo Ellis Kahn, Francis S. Collins, *Genetic Discrimination and Health Insurance: An Urgent Need for Reform*, 270 Science 391 (1995); Robert J. Pokorski, *Genetic Information and Life Insurance*, 376 Nature 13 (1995). Employers likewise can use genetic information to make employment decisions, such as hiring, firing, or promotion. *Council on Ethical and Legal Affairs, American Medical Association, Use of Genetic Testing by Employers*, 266 J.A.M.A. 1827 (1991). Discrimination risks are being addressed by a growing number of states,

as researchers are quick to point out, securing consent from persons whose tissues were taken for clinical or research purposes in the past is difficult because of concerns about privacy, problems in locating and contacting individuals, and questions about the need for consent and the protection of human subjects when the source of the tissues has died but relatives are available who might have valid interests in the use of tissues that can yield information about them.

Because of these difficulties, investigators who wish to use stored tissues in their research may avoid the burden of securing prior consent either by having their research exempted from the oversight and consent requirements of the federal rules⁸ regulating human subjects experimentation for all federal agencies (except for the Food and Drug Administration) or by having the need for informed consent waived by their Institutional Review Boards (IRBs). Under these rules, research may be exempt from human subjects review if it entails the⁹

study of existing data... [and] pathological specimens or diagnostic specimens... if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

This requires that samples used in research have all identifying information removed and disassociated from the tissues by removing any linking codes that could permit investigators or anyone else associated with the research to identify individual subjects.

Alternatively, researchers may ask IRBs to waive the informed consent requirements. Informed consent may be modified or waived if the IRB finds that the research presents only minimal risk to subjects, that the waiver of consent will not adversely affect the rights or welfare of subjects, that the research could not practicably be carried out without the waiver, and that subjects will be provided information about their participation afterwards, when appropriate.¹⁰ Further, if a

but social stigmatization is beyond the reach of such laws.

⁸ 45 C.F.R. § 46.101-409 (1996).

⁹ 45 C.F.R. § 46.101(b)(4).

¹⁰ 45 C.F.R. § 46.116(d) (1996). "Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." 45 C.F.R. § 46.102(i).

protocol involving the study of existing data, pathological specimens, or diagnostic specimens raises no more than minimal risk, then the decision about waiver may be made on an expedited basis by the IRB chair or by one or more experienced reviewers designated by the chair.¹¹ If so approved, then research may proceed with linked or even directly identified tissues.

Waiver of informed consent and expedited review are predicated upon the determination that the research poses no more than minimal risk. It is clear that, in the past, just about any research involving the study of existing pathological or diagnostic specimens was broadly considered to “present no more than minimal risk to subjects.”¹² Yet, explicit in the recent analyses of Annas,¹³ Clayton et al.,¹⁴ and others is that the risks posed by germ-line genetics research with stored tissues are greater than minimal, if subjects are identifiable.¹⁵ Identifiable means that individual identity is manifest with the tissue or data or that individuals can be identified by use of a linking code. If the risks of research with stored tissues are not minimal, then either complete de-identification and de-linking of tissues to render them irreversibly anonymous or express consent from subjects is necessary before using those tissues in germ-line genetics studies.

We decided to explore whether those with experience in biomedical research and bioethics perceive the riskiness of genetics research as being more than minimal. We also wanted to examine whether the problems posed by genetics research and storage of tissues are salient to persons in these communities.

¹¹ 45 C.F.R. § 46.110 (1995).

¹² 46 F.R. 8366–8391, 8380 (January 26, 1981).

¹³ *Supra* note 5.

¹⁴ *Supra* note 5.

¹⁵ See e.g., Jon F. Merz, *Is Genetics Research “Minimal Risk”?* 18(6) IRB: Rev. Human Subjects Res. 7 (1996) (discussing substantive differences between clinical and research genetics activities and the evolving standard of prior counseling and informed consent in clinical use of these technologies); Philip R. Reilly, Mark F. Boshar, Steven H. Holtzman, *Ethical Issues in Genetic Research: Disclosure and Informed Consent*, 15 *Nature Genet.* 16, 19 (1997) (noting that past judgments of minimal risk are probably inadequate for genetics research studies).

The Questionnaire

We developed a simple questionnaire, presenting extremely general descriptions of two research protocols involving a blood draw:

A. How risky to healthy adult subjects do you believe biomedical research is which involves the collection of a single vial of blood for research on the causes of disease?

B. How risky to healthy adult subjects do you believe biomedical research is which involves the collection of a single vial of blood for storage and use in future research on the role of germ-line genetic mutations in causing disease?

We first asked respondents to rate the “riskiness” of the protocol. The activities of Protocol B are implicitly subsumed in those circumscribed by Protocol A. That is, when blood is taken for the purpose specified in Protocol A, excess tissue will often be stored and may be available for future studies as described by Protocol B. Arguably the risks of Protocol A should be comparable or marginally larger because the description covers a broader category of research. Nonetheless, because we did not believe that respondents would think of the secondary uses of blood taken for one purpose, we hypothesized that respondents would be more likely to identify the risks associated with generation of genetic information and loss of confidentiality in Protocol B and rate it as more risky than Protocol A.

We also asked respondents to identify any risks or consequences that came to mind when judging the riskiness of each protocol. We hypothesized that respondents who identified any risks arising from the generation of genetic information (which we term “genetics risks”, including, e.g., stigmatization, insurer or employer discrimination, breach of confidentiality, and discovery of unwanted and uncertain information about future disease risks) would rate the riskiness of each protocol higher than respondents who did not identify those risks.

Finally, we asked respondents their age, gender, education, and whether they have ever served on an IRB. IRB approval was secured for a pilot study and for a survey of subscribers to the “mcwbioethics” and “mcw-irb” discussion lists maintained at the Medical College of Wisconsin (MCW). These two studies varied in design, and are described separately below. The main hypotheses were to be examined by analysis of variance and linear regression.

Pilot Study

Method

The questionnaire was piloted with attendees of the NCIC/Terry Fox and Health Canada Workshop on Tumor Tissue Banks held in Toronto in mid-April, 1996. A "between-subject" design was used, and a questionnaire presenting either Protocol A or B was placed in attendees' information packets. Surveys were collected throughout and after the workshop. No compensation was offered to respondents.

Responses to the risk rating question was elicited with the scale shown in Figure 1.

Figure 1
Scale Used for Risk Elicitation in the Pilot Study

+-----+	+-----+	+-----+	+-----+	+-----+	+-----+
no	minimal	low	medium	high	very high
risk	risk	risk	risk	risk	risk

Results

There were 65 attendees from various institutions throughout Canada, with several individuals from the US. Twenty nine responses (45%) to the questionnaire were collected. Respondents on average were 44 years of age (standard deviation (SD) = 6.8, range 33–60), seventeen were male (59%), 24 (83%) had an MD degree, and 10 (34%) had IRB experience. Sixteen respondents received Protocol A, and 13 received Protocol B. Twenty respondents (69%) identified genetics risks in the protocols, and there was no difference in the fraction doing so based on which question they received.

There was no main effect of protocol form on risk judgments. This most likely occurred because many respondents filled out the questionnaire shortly after two plenary speeches on the ethical issues of tissue banking, including one by the author, which were given at the beginning of the meeting. There was, however, a strong main effect on risk judgments with identification of any genetics risks. Respondents who identified those risks on average rated the risk 1.2 ratings higher than others (Mann-Whitney test $Z = -2.34$, $p = 0.02$).

Exploratory regression analysis suggested no relationship between risk ratings and age, whether the respondent held an MD or not, or IRB experience. There was weak evidence that female respondents had a

tendency to rate the risks higher than males, with an average risk evaluation for females identifying the genetics risks of 1.3 ratings higher than males likewise identifying those risks (Mann-Whitney test $Z = -1.42$, $p = 0.15$).

This pilot suggested that the questions were understandable to respondents. To increase our power to study our first hypothesis, we decided to perform a "within-subject" study.

Discussion Group Survey

Method

Permission was granted by the moderators of the MCW Bioethics Discussion Forum and the MCW Institutional Review Board Forum to solicit list subscribers for participation in the survey. We posted an introductory paragraph inviting subscribers to complete the survey. Protocol A was then presented along with the question asking respondents to identify the risks that came to mind when responding and questions eliciting demographic information (age, gender, highest degrees and past or present IRB experience). The instructions asked respondents to respond to the author, not the list, and specified that this was the first part of a two-part survey. No compensation was offered for participation.

The scale in Figure 2 was used to elicitate risk ratings. When subscribers responded, Protocol B was emailed directly to them with the risk scale and the risk identification question. Presentation order was unvaried because the intent was to see how salient were risks from genetics research in the generally described protocol.

Figure 2

Scale Used for Risk Elicitation in the Bioethics and IRB Forum Surveys.

- 1 no risk
- 2 minimal risk
- 3 a minor increase over minimal risk
- 4 low risk
- 5 medium risk
- 6 high risk
- 7 very high risk

Results

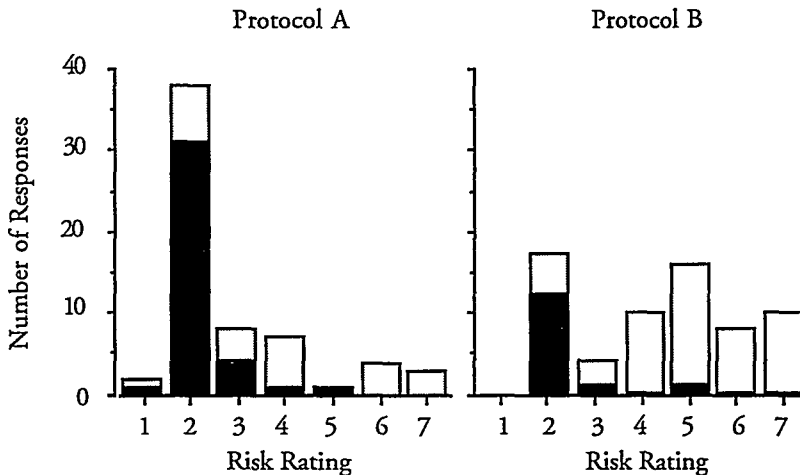
The survey was posted to an estimated 811 subscriber list. A total of 96 responses was received to the first survey question (12%). These respondents were treated as a convenience sample because of their availability and likely interest, not because they are representative of the greater sample either of subscribers to these lists, IRB members or staff, or bioethicists generally. Of the 96 respondents, eight stated that one or both protocols were too ambiguous to provide risk judgments or provided alternative assessments based on subject identifiability or linkage of identities and whether the research was genetic in nature. Also, sixteen who responded to the first question did not respond to the second. Responses of these two groups were omitted from further analysis. Two days after the survey was posted, a response was posted back to the entire list, and Protocol B was mistakenly posted by the author to the entire list instead of back only to the respondent. Because of the risk of contamination of the results, enrollment was curtailed thereafter, and the responses of an additional four individuals were omitted from further analysis. In sum, a total of 68 responses were received containing at least one risk judgment; 60 respondents provided numerical risk judgments for both protocols. Risk ratings that were given as ranges of values were coded at the midpoint value.

Respondents were on average 44 years of age ($SD = 9.3$, range 24–73). Forty one respondents were male (60%), fourteen (21%) hold an MD, ten (15%) hold a law degree, 32 (47%) hold a PhD, and 55 (81%) currently serve or have served on an IRB. Female respondents were slightly less likely than males to hold an MD (2 (7%) of 27; continuity corrected $\chi^2 = 3.52$ with 1df, $p = 0.06$) or a PhD (7 (22%) of 27; $\chi^2 = 8.03$ with 1 df, $p = 0.005$).

Our first hypothesis was that respondents would rate Protocol B as more risky than Protocol A. The mean risk rating of Protocol A was 2.9 ($SD = 1.5$, range 1–7), and the mean risk rating of Protocol B was 4.4 ($SD = 1.8$, range 2–7). This difference is significant (Mann-Whitney test $Z = -4.80$, $p < 0.0001$) and supports our hypothesis. A histogram of responses is provided in Figure 3. Risk categories are listed along the X-axis. This figure shows the total number of respondents who chose each risk value for Protocol A, on the left, and Protocol B, on the right. The

darker portion of each column shows the number of respondents picking that risk value who identified no or only physical risks and the lighter shows the number that identified any genetics risks. The distribution of risk ratings of Protocol A has a mode of 2, while the distribution of ratings of Protocol B has modes of 2 and 5.

Figure 3



The second hypothesis was that respondents would rate the riskiness of each protocol as higher if they identified any genetics risks in the protocols. Protocol B was designed to elicit those risks. Our test of this hypothesis has two parts. First, we examine whether there is a difference in the risk ratings on protocols A and B between respondents who identified any genetics risks for each protocol and those who did not. Of 63 responses on Protocol A, 38 (60%) identified no or only the physical risks of a blood draw (including pain, hematoma, infection, bleeding, fainting, and nerve or tissue damage), and their mean risk rating was 2.2 (SD = 0.7). Twenty-five respondents (40%) identified some genetics risks, and their average riskiness rating of the protocol was 3.9 (SD = 1.9). Again, this is a significant difference between these groups (Mann-Whitney test $Z = -4.19$, $p < 0.0001$).

Of 65 responses on Protocol B, 14 (22%) identified no or only the physical risks with a mean risk rating of 2.3 (SD = 0.8), and 51 (78%) identified genetics risks with a mean risk rating of 5.0 (SD = 1.5). This is again a significant difference (Mann-Whitney test $Z = -4.82$,

$p < 0.0001$). Also, as we hypothesized, while 30 of 68 respondents (44%) identified genetics risks in Protocol A, 53 of 68 (78%) did so on Protocol B ($\chi^2 = 16.4$ with 1 df, $p < 0.0001$). No respondents who identified a genetics risk on Protocol A failed to do so on Protocol B. These differences in risk ratings are apparent in Figure 3. For both protocols, the risk ratings for those identifying any genetic risks are distributed more broadly and higher on the response scale.

Second, to explore whether any demographic factors were related to respondents' risk judgments, linear regression was used. This analysis showed that risk ratings on Protocol A were related significantly only to whether or not respondents identified any genetics risks. Further, we examined respondents' differential risk judgments for the 60 respondents who provided numerical risk values for both protocols.

Figure 4¹⁶

Protocol B Responses	7	1	2			1	2	3
	6		3				2	
	5	1	9	3	4			
	4		4	2	1	1		
	3		1	2	1			
	2		16	1				
	1							
		1	2	3	4	5	6	7
Protocol A Responses								

The differential was calculated by subtracting respondents' risk judgments on Protocol A from their judgments on Protocol B. Individuals' responses to the two protocols are shown in Figure 4. A linear regression model showed that: (1) respondents' risk judgments

¹⁶ The number of respondents whose Protocol B risk ratings (2–7) followed initial Protocol A risk ratings (1–7). Differential risk ratings are the rating given for Protocol B less that given for Protocol A for each respondent.

shifted more between Protocol A and Protocol B if they initially identified any genetics risks on Protocol A ($\beta = 2.2$, $t = 5.05$, $p < 0.0001$), mediated by an initial higher risk ratings of Protocol A ($\beta = -0.57$, $t = 5.10$, $p < 0.0001$); and (2) respondents who initially failed to identify the genetics risks on Protocol A but did so on Protocol B shifted their risk judgments a great deal ($\beta = 1.4$, $t = 3.11$, $p = 0.003$), and female respondents who did this rated the risks of Protocol B much higher than did males ($\beta = 1.6$, $t = 2.68$, $p = 0.01$).

Discussion

These studies suggest that respondents on average perceive risks from germ-line genetics research with identified human tissues as substantially greater than minimal. Such research involves the generation of information about individuals and family members, posing risks from possible breaches of confidentiality and disclosure of information to those who do not want to, or who have no right to, know. The results also suggest that when tissues are stored in a manner permitting identification of individuals, then the mere availability of the tissues may be perceived as posing more than minimal risk because of the uncertainty about the uses to which they might be put.

If the storage of tissues for future studies of germ-line genetic mutations presents more than minimal risk to identifiable subjects, then special attention should be given to any clinical or research practices from which excess human tissues will be potentially available for future research. While most research with stored tissues currently does not involve study of germ-line genetic mutations, there appears to be increasing demand as genetic technology burgeons. This has implications for the use of previously collected tissues, as well as for the prospective collection of tissues for both clinical and research purposes.

First, it seems clear from these results that germ-line genetics research using stored tissues should only proceed either with the fully informed consent of identifiable subjects, or in the alternative, with tissues that have been completely and irreversibly de-identified or made anonymous. Waiver of consent in protocols using identifiable tissues is not permissible ethically or under the federal rules when the research poses more than minimal risk to subjects.

Second, for prospective collection of samples exclusively for research or as an adjunct to clinical care, informed consent of subjects is required, as is review of proposed research protocols by the full IRB. Because of the simple procedures involved in collecting blood or other DNA-bearing tissues, research involving them often has been classified as minimal risk and therefore eligible for expedited review without detailed examination of the specific protocol. This is no longer appropriate, because genetic technology raises unique information-related risks. Protocols involving prospective collection of tissues must address issues of tissue disposition, and if storage is planned, express informed consent to that storage should be secured.

A possible critique of the survey of discussion forum participants presented here is that very few of the list subscribers actually responded to the survey. However, we treat the respondents as a convenience sample, and we need not extrapolate these results to be generalized to the surveyed population (or to the greater population of bioethicists, lawyers, and clinician/researchers interested in these issues, who are likely not truly represented on all relevant dimensions by those who subscribe to the discussion groups). Rather, these results reflect in part the perceptions of the risks of tissue storage and genetics research held by a learned and interested group of individuals who self-selected to respond to the survey.

We used a "within-subject" experimental manipulation to specifically study whether the risks attendant to storage of identifiable tissues and potential use in germ-line genetics studies are salient, and whether individuals think the genetics-related risks are more than minimal. Less than half (44%) of the respondents initially identified the risks attendant to germ-line genetics studies in a general statement about research of the causes of disease, while 78% did so when the protocol specifically called for storage for future use in such studies. The study manipulation effectively got subjects to address the genetics-related risks, and a majority of them (74%) rated the riskiness of the storage of blood in identified form for use in future genetics research as greater than minimal. One primary concern about these results is that more respondents did not perceive the genetics-related risks and rate these risks as greater than minimal, but this is not unexpected given broad

differences in individual risk perceptions and the rapidity with which genetic technologies — and societal responses thereto — are evolving.

Another possible critique of this study is that the research protocols described to subjects were too vague to elicit meaningful responses. Certainly, no IRB would approve any protocol submitted to them in such general terms. Nonetheless, the extreme generality of the described protocol was necessary to get people to think about the uses to which a simple blood sample could be put. Many respondents did just that, raising questions about what would be done, including in particular concerns about whether the samples would be identified or linked with subjects' identities and whether they would be used in genetics research. Others focused on the physical risks of a blood draw, and their limited focus on that procedure highlights the purpose of this study. Until expressly spelled out, the risks from potential uses for excess tissues — storage of which is a common practice in many clinical laboratories — was not salient to more than half of the respondents on the first protocol.

Had we presented a detailed protocol describing the planned research, the issue of disposition of the excess sample would have been less salient, as it is in real research. Simply, protocols are complex, and IRBs already have many issues they must address, often involving life and death and severe health risks from diseases and innovative medical care. Information related risks, conditional upon future studies performed with inadequate protections for identifiable subjects, may just not be substantial enough to earn an IRB's attention. Yet, disposition of tissues is important and must be addressed explicitly at the time of IRB approval, before securing informed consent and collecting samples. Research, as well as the IRB's review, might be facilitated by developing institution-wide procedures for managing human tissues in clinical care and research, addressing the concerns raised by the prospects for future uses of identifiable tissues.¹⁷

¹⁷ One model for protecting subjects is to create an institutional tissue trustee, who may establish a one-way link between clinical information and tissue sources and research resources, ensuring that researchers cannot identify individual subjects and that information generated in research is prevented from flowing backwards towards the clinical record. See, Jon F. Merz et al., *Use of Human Tissues in Research: Clarifying Clinician and Researcher Roles and Information Flows*, 45 J. Investigative Med. 252 (1997).

Conclusion

Genetics technology has unleashed a new set of concerns regarding uses of potentially generated medical information. These concerns make it more important to protect the confidentiality of information and to plan — before the research is done — for the types of information apt to be generated and to plan what will be done with that information. Whether using tissues taken from people for a specific research project or tissues left over from clinical or other research uses, issues about the specific consent of subjects to use of identifiable materials in genetics research must be addressed by investigators and IRBs. Recent commentary strongly suggests that germ-line genetics research poses more than minimal risk to identifiable subjects (including the person from whom the tissues were taken as well as family members to whom any genetic information may apply), and most of the respondents in this survey agreed. Moreover, storage of tissues in identifiable form itself raises concerns about future uses, perhaps posing more than minimal risk to people because of the uncertainty about what might be done with those tissues. Thus, clinicians and investigators need to think about their methods of storing and using tissues or making them available to other researchers for study. If excess tissues will not be needed for clinical care, then identifiers and linking codes should be destroyed. At the least, patient consent for storage and recontact can be secured at the time the tissues are obtained, if use of the tissues is foreseeable. Investigators and IRBs should explicitly consider the disposition of excess tissues collected — from archives or from human subjects — in planned research, and take steps to minimize the confidentiality and information-related risks in approved protocols.

