

## Stored Tissue

**Goal:** To develop an analysis of the ethics of research on stored samples, and assess specific ethical issues that arise in the conduct of such research by collecting appropriate empirical data.

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**Background:** Recent advances in genetics and biomedical technologies have dramatically increased the scientific value of the hundreds of millions of human tissue and blood samples stored in laboratories across the country and around the world. This increased value has engendered a continuing debate over whether investigators should be required to obtain individuals' informed consent before conducting research on currently stored human biological materials, and how consent should be obtained for the collection of new materials that might be used for research purposes.

Existing regulations and guidelines on clinical research offer little assistance for answering these questions. The Federal regulations focus on research that involves direct interaction with subjects, leaving it unclear to what extent they apply to research on stored samples. Further, these regulations do not specify what information should be disclosed prior to obtaining subjects' consent for collection of new research samples.

Determining whether investigators should obtain subjects' informed consent is made difficult by several considerations. First, most stored biological samples were obtained as part of clinical care, without any indication of whether they might be used for future research purposes. Even samples obtained as part of individuals'

previous research participation often do not include indications of whether they can be used for *future* research, and what types of research.

Second, the principal risks of research on stored biological samples involve unwanted information flow. Such research may reveal facts about the sources and their futures, that they did not know, and did not want others—employers, insurers, or family members—to know. Unfortunately, there are almost no data on the magnitude of these risks.

The existing arguments for whether investigators should be required to obtain consent for research on stored biological samples take two general approaches. Many commentators argue that the determination of whether consent should be obtained depends on the risks involved. Since the risks vary depending upon the type of samples in question, this view leads to different consent standards for research on different types of samples. In particular, stored biological samples may be of three general types: ‘identified’ (attached to personal identifiers), ‘coded’ (linked to personal identifiers through a coding scheme) or ‘anonymous’ (not linked to any personal identifiers).

According to the American Society of Human Genetics (ASHG), anonymizing samples protects sources from risks and thus “eliminates the need for recontact to obtain informed consent.” Similarly, the U.S. Federal regulations (“Common Rule”) explicitly exempt research on stored biological samples from IRB review, and other regulatory safeguards, provided the sources cannot be “identified directly or through identifiers linked to the samples” (46.101).

Critics respond that this approach misunderstands the reason for obtaining informed consent. Informed consent is important because it allows sources to control whether their samples are used for research purposes. In the words of a United States NIH-DOE ELSI working group: “If research is done on a sample for which the source can be identified, that source should be asked for his or her consent.” On this view, investigators should obtain sources’ consent whenever possible.

Those who argue for obtaining sources’ consent disagree about exactly what individuals should consent to. Some argue that research on biological materials is ethically acceptable only when the subjects explicitly give consent for the samples to be used to study the disease in question. Others argue that investigators should not share samples with other research teams unless subjects explicitly consented to such sharing and, perhaps, even specify precisely which investigators may use the samples.

Research on human biological materials also raises a question of whether ‘sources’ should be informed of results of uncertain clinical significance. Researchers often do not have a clinical relationship with sources, and sources may misinterpret research results of uncertain clinical significance. For these reasons, the U.S. National Bioethics Advisory Commission (NBAC) argues that the need to inform sources usually “does not apply to research using human biological materials.” Others argue that investigators should provide sources with information gained about them.

**Objectives:**

- 1) To assess empirically individuals' views regarding research on human biological materials, and determine to what extent individuals believe their consent should be obtained for such research
- 2) To assess empirically what restrictions, if any, individuals would place on the future research use of samples obtained from them.
- 3) To assess empirically to what extent individuals want to receive information obtained during research that is of uncertain clinical significance.
- 4) To assess empirically whether individuals' views on research with human biological materials vary by sociodemographic characteristics, disease, or attitudes about privacy, trust, or research.
- 5) To assess empirically IRB and investigator practices with regard to informed consent for research on human biological materials
- 6) To assess conceptually the extent to which the debate over the ethics of research on stored samples suggests a new model for understanding research participation in general.

**Methodology:** The proposed safeguards concerning research on human biological materials are typically based on conceptual considerations. However, these recommendations almost invariably rely on assumptions concerning what subjects want, hence, what proper respect for subjects requires. For instance, the proposal that sources should be asked to provide consent for research conducted on other diseases assumes that individuals are more willing to have their samples used for research on the condition from which they suffer.

To assess the accuracy of these assumptions it is important to survey various groups of individuals to understand their views regarding research on stored biological samples: When do individuals think consent should be required? Do they think it is more important to obtain consent for future research on other diseases than the disease for which the sample was originally obtained? Do individuals want to control which investigators may conduct research on their samples? Do individuals want to receive information of uncertain clinical significance?

With respect to current practice, it is important to understand what information is provided to subjects as part of the informed consent process, and what choices research subjects actually make when given choices regarding the future use of their samples.

Finally, most guidelines on research with human biological are based on whether the samples were previously obtained, or will be obtained in the future. Existing regulations, such as the U.S. Federal regulations, are more likely to require consent for research on stored samples that will be obtained in the future. This approach is common, but somewhat surprising given the standard view that risks are the operative consideration for determining whether consent should be required. In particular, whether the samples were obtained previously, or will be obtained in the

future, does not necessarily influence the risks of the research. Conceptual analysis of the possible relevance of when samples are obtained might shed light on additional ethical considerations underlying such research.

**Results:** To assess individuals' views regarding research on stored samples, we conducted a telephone survey of 504 individuals. Two cohorts were studied: 1) individuals who had participated in clinical research and contributed biological samples, and 2) randomly selected Medicare recipients. Overall, 65.8% of respondents would require their consent for research on clinically derived, personally identified samples; 27.3% would require their consent for research on clinically derived samples that would be anonymized. For research derived samples, 29.0% would require their consent if the samples retain personal identifiers; 12.1% if the samples would be anonymized before the research is conducted. 88.8% want to be informed of results of uncertain clinical significance. 91.9% would not impose greater safeguards on future research on a different disease. These data suggest that current practice and policy recommendations regarding research using stored biological samples may be inconsistent with sources' preferences in several respects. In particular, it appears that most sources want to control whether their samples are used for research purposes, are not concerned with the particular disease that will be studied, and want to receive results of uncertain clinical significance. Follow-up research will be needed to assess the generalizability of these data.

We have recently completed an evaluation of how research on stored samples is presented on consent forms at the NIH Clinical Center. The consent forms for 832 protocols were assessed. Of these, 258 discussed genetics research or future use of samples. Risks were mentioned in 62% of the forms; whether results would be shared was mentioned in 67%. The specific risk related to identification of misattributed paternity was mentioned in 80% of forms involving family studies, and 44% of forms that involved individuals only. In the latter case, this risk is almost nonexistent. Secondary use of samples was mentioned in 89% of forms. Subjects were given options to specify the conditions of future research in 18% of forms. However, there was wide variation in the specific options provided. These findings suggest that the actual process of informed consent for research on stored samples varies widely, and sometimes omits important information, such as risks, and other times includes irrelevant information.

We also assessed the actual choices individuals at the NIH clinical center made concerning future research use of their samples from 1/1/00-6/1/02. During this time, 1350 individuals made choices as part of 89 active protocols. 89% allow future research on the same disease; 85% allow future research on different diseases; 3% did not allow any future research on their samples. These data support the view that the vast majority of individuals do not regard the distinction between their disease and other diseases as morally relevant.

We have also conducted a conceptual analysis to understand the underlying views of informed consent that give rise to the varied recommendations and guidelines. Most guidelines and recommendations are based on the importance of protecting subjects from risks, or the importance of respecting individuals' ability to control what happens to their bodies. Conceptual analysis of the relevance of when samples are obtained suggests a new model of research participation. On this model, it is important to consider the interests subjects might have in determining to which projects they contribute. This model suggests that the role of informed consent is wider than typically recognized.

**Future Directions:** To assess individuals' views on the use of their samples for research on diseases unrelated to the disease for which the samples were originally obtained we asked respondents about future research on *diabetes*. We plan to assess whether individuals are more likely to regard the distinction between their disease and other diseases as morally relevant when the other disease is specified as one with more negative social connotations, such as alcoholism or depression. In addition, it will be important to determine under what conditions, if any, individuals regard as relevant who will be conducting the research in question.

Our survey of individuals' attitudes enrolled very few minorities. To assess whether our findings generalize, we are collaborating with Emory University, and Grady Hospital of Atlanta, to assess minorities' views on research with stored samples.

We are currently conducting telephone surveys of 1200 individuals from Maryland, North Carolina, Utah, and Arizona regarding attitudes about current and future uses of samples. These sites were selected to recruit a population with a broad ethnic and racial diversity. The potential respondents are being recruited from general medical clinics, oncology clinics and thoracic surgery clinics, as well as people who have given blood for genetics research.

### **Publications:**

Wendler D, Emanuel E. The debate over research on stored biological samples: what do sources think? Archives of Internal Medicine 2002; 162:1457-1462.

Wendler D. What research with stored samples teaches us about research with human subjects. Bioethics 2002; 16:33-54.