RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIALS: ETHICAL ISSUES AND POLICY GUIDANCE

VOLUME I

Report and
Recommendations
of the
National Bioethics
Advisory Commission

Rockville, Maryland
August 1999

The National Bioethics Advisory Commission (NBAC) was established by Executive Order 12975, signed by President Clinton on October 3, 1995. NBAC's functions are defined as follows:

a) NBAC shall provide advice and make recommendations to the National Science and Technology Council and to other appropriate government entities regarding the following matters:

   1) the appropriateness of departmental, agency, or other governmental programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior; and

   2) applications, including the clinical applications, of that research.

b) NBAC shall identify broad principles to govern the ethical conduct of research, citing specific projects only as illustrations for such principles.

c) NBAC shall not be responsible for the review and approval of specific projects.

d) In addition to responding to requests for advice and recommendations from the National Science and Technology Council, NBAC also may accept suggestions of issues for consideration from both the Congress and the public. NBAC also may identify other bioethical issues for the purpose of providing advice and recommendations, subject to the approval of the National Science and Technology Council.

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Table of Contents

Letter of Transmittal to the President

National Bioethics Advisory Commission

National Bioethics Advisory Commission Staff and Consultants

Executive Summary i

Chapter 1: Overview and Introduction 1

The Use of Human Biological Materials in Research 1

The Research Value of Human Biological Materials 1

Is Genetic Information Different from Other Medical Information? 3

Increasing Discussion About the Appropriate Research Use of Human Biological Materials 4

About This Report 9

Notes 10

References 11

Chapter 2: Collection, Storage, and Use of Human Biological Materials in the United States 13

Collections of Human Biological Materials 13

Identifiability of Human Biological Materials 15

The Value of Human Biological Materials to Current Research 19

Summary 23

Notes 24

References 24

Chapter 3: Current Guidance on the Use of Human Biological Materials in Research 27

Introduction 27

Scope of the Current Federal Regulations 27

Medical and Scientific Organization Standards and Guidance 32

International Perspectives on the Use of Human Biological Materials in Research 33

Publication Guidelines 34

Medical Record Protection 35

Summary 38

Notes 39

References 40

Chapter 4: Ethical Perspectives on the Research Use of Human Biological Materials 41

Introduction 41

Promoting Benefits and Minimizing Harms and Wrongs 42

Potential Harms from Breaches of Privacy and Confidentiality 43

Group-Related Harms 46

Respecting Persons Who Are Sources of Biological Materials 47

Just Institutions, Policies, and Practices 49

Commodification of the Body and Its Parts: Issues of Justice and Respect for Persons 50

Summary 51

Notes 52

References 52

Chapter 5: Conclusions and Recommendations 55

Introduction 55

Research Governed by the Federal Regulations: Activities Beyond Clinical Care 56

Interpretation of the Existing Federal Policy for the Protection of Human Subjects 57

Expedited Review 60

Special Concerns About the Use of Unlinked Samples 60

Requirements for Investigators Using Coded or Identified Samples 62

Using Previously Obtained Informed Consent and Reconsent 62

Obtaining New Consent 63

Criteria for Waiver of Consent 66

Rendering Existing Identifiable Samples Unidentifiable to Avoid the Need for Consent 70

Reporting Research Results to Subjects 71

Considerations of Potential Harms to Others 72

Publication and Dissemination of Research Results 73

Professional Education and Responsibilities 74

Use of Medical Records in Research on Human Biological Materials 74

Summary 75

Notes 75

References 76

Appendices

Appendix A: Beliefs About the Research Use of Human Biological Materials 77

Appendix B: Code of Federal Regulations, Title 45, Part 46 81

Appendix C: Comparison Table of Professional Statements 99

Appendix D: Guidance for Institutional Review Boards Reviewing Research Using Human Biological Materials 105

Appendix E: Public Comments on NBAC's February 22, 1999, Draft 111

Appendix F: Public and Expert Testimony 113

Appendix G: Commissioned Papers 115

NATIONAL BIOETHICS ADVISORY COMMISSION

July 16, 1999

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The President
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Dear Mr. President:

On behalf of the National Bioethics Advisory Commission (NBAC), I am pleased to transmit our third report to you: *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance.* This report addresses a topic that follows from the priorities established in Executive Order 12975—to consider the rights and welfare of human research subjects and the management and use of genetic information.

In this report, NBAC addresses an issue at the confluence of two important developments. The first development is the remarkably enhanced ability of biomedical researchers to study human biological materials, such as biopsy specimens obtained for diagnostic purposes, organs and tissues removed during surgery, and biological materials collected in research projects; to increase knowledge about human diseases; and to develop better means to prevent, diagnose, and treat these diseases. NBAC has estimated that there are more than 282 million such specimens in the nation's laboratories, tissue repositories, and health care institutions. The ability to use these materials in research in striking new ways will provide even more effective tools for improving health. Yet, the very power of these new research tools raises a number of important ethical issues.

The second development is the increasing concern that the use of genetic and other medical information found in these materials might infringe upon an individual's privacy, and if misused could result in discrimination—issues that you addressed in your remarks in the East Room on July 17, 1997. Because medical research using these specimens can reveal clinical and sometimes personal information about individuals, scientists must ensure that those who participate in research by providing these materials are adequately protected from unwarranted harms resulting from the inadvertent release of such information.

NBAC focused its deliberations on the following questions: How well does the existing Federal Policy for the Protection of Human Subjects (the Common Rule, codified at 45 CFR Part 46) meet the objective of protecting human subjects from harm in research involving human biological materials? Specifically, does it provide clear direction to research sponsors, investigators, IRBs, and others regarding the conduct of research using these materials in an ethical manner?

While the overall structure of the federal regulations is generally satisfactory for addressing this area of research, NBAC concluded that the Common Rule was not entirely responsive to these questions. In some cases, present regulatory language provides ambiguous guidance for research using human biological materials. For example, researchers are often unclear whether research on human tissue makes the people from whom it came "human subjects," and IRBs struggle to determine whether research on these samples poses more than a "minimal risk" to these people. Beyond these ambiguities, certain parts of current regulations are inadequate to ensure the ethical use of human biological materials in research and require some modification.

NBAC concluded that not only is it critical that human biological materials continue to be available to the biomedical research community, but, increasingly, it is essential for investigators to collect human biological materials from individuals who are also willing to share important ongoing clinical information about themselves. Policies and guidelines governing human subjects research should permit investigators—under certain circumstances and with the informed, voluntary consent of sample sources—to have access to identifying information sufficient to enable them to gather necessary data regarding the subjects. Provided that adequate protections exist (which usually, but not always, include informed consent), such information gathering could include ongoing collection of medical record data and even requests for individuals to undergo tests to provide additional research information. In some cases, it even will be acceptable for investigators to convey information about research results to the persons whose samples have been studied. Where identifying information exists, however, a well-developed system of protections must be implemented to ensure that risks are minimized and that the interests of sample sources are protected.

In this report, NBAC makes 23 recommendations to address the following concerns: addressing perceived difficulties in the interpretation of federal regulations and in the language of position statements of some professional organizations; ensuring that research involving human biological materials will continue to benefit from appropriate oversight and IRB review, the additional burdens of which are kept to a minimum; providing investigators and IRBs with clear guidance regarding the use of human biological materials in research, particularly with regard to informed consent; providing a coherent public policy for research in this area that will endure for many years and be responsive to new developments in science; and providing the public (including potential research subjects) with increased confidence in research. In particular, this report provides interpretations of several important concepts and terms in the Common Rule and recommends ways both to strengthen and to clarify the regulations and to make their implementation more consistent.

These recommendations benefited tremendously from the input of and consultation with scientists, research administrators, and the public. This report is a testament to the knowledge of and interest in these issues by patients, the research community, and professional organizations; their input helped inform the Commission's thinking and the report as a whole.

On behalf of the Commission, we appreciate the opportunity to transmit this report to you.

Sincerely,

Harold T. Shapiro
Chair

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*Until May 1999

Executive Summary

Introduction

Biomedical researchers have long studied human biological materials—such as cells collected in research projects, biopsy specimens obtained for diagnostic purposes, and organs and tissues removed during surgery—to increase knowledge about human diseases and to develop better means of preventing, diagnosing, and treating these diseases. Today, new technologies and advances in biology provide even more effective tools for using such resources to improve medicine's diagnostic and therapeutic potential. Yet, the very power of these new technologies raises a number of important ethical issues.

Is it appropriate to use stored biological materials in ways that originally were not contemplated either by the people from whom the materials came or by those who collected the materials? Does such use harm anyone's interest? Does it matter whether the material is identified, or identifiable, as to its source, or is linked, or linkable, to other medical or personal data regarding the source? The extent to which a research sample can be linked with the identity of its source is a significant determination in assessing the risks and potential benefits that might occur to human subjects. For this reason, the National Bioethics Advisory Commission (NBAC) has developed a schema to describe the character of the personal information associated with particular samples of human biological materials as they exist in clinical facilities or other repositories and in the hands of researchers. (See Table 1.)

Ethical researchers must pursue their scientific aims without compromising the rights and welfare of human subjects. However, achieving such a balance is a particular challenge in rapidly advancing fields, such as human genetics, in which the tantalizing potential for major advances can make research activities seem especially important and compelling. At the same time, the novelty of many of these fields can mean that potential harms to individuals who are the subjects of such research are poorly understood and hence can be over- or underestimated. This is particularly true of nonphysical harms, which can occur in research conducted on previously collected

Table 1: Categories of Human Biological Materials

Repository Collections

Unidentified specimens: For these specimens, identifiable personal information was not collected or, if collected, was not maintained and cannot be retrieved by the repository.

Identified specimens: These specimens are linked to personal information in such a way that the person from whom the material was obtained could be identified by name, patient number, or clear pedigree location (i.e., his or her relationship to a family member whose identity is known).

Research Samples

Unidentified samples: Sometimes termed "anonymous," these samples are supplied by repositories to investigators from a collection of unidentified human biological specimens.

Unlinked samples: Sometimes termed "anonymized," these samples lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being.

Coded samples: Sometimes termed "linked" or "identifiable," these samples are supplied by repositories to investigators from identified specimens with a code rather than with personally identifying information, such as a name or Social Security number.

Identified samples: These samples are supplied by repositories from identified specimens with a personal identifier (such as a name or patient number) that would allow the researcher to link the biological information derived from the research directly to the individual from whom the material was obtained.

human biological materials when investigators do not directly interact with the persons whose tissues, cells, or DNA they are studying.

Increasing concerns about the use of genetic and other medical information have fueled the current debate about medical privacy and discrimination. Because medical research can reveal clinically relevant information about individuals, scientists must ensure that those who participate in research are adequately protected from unwarranted harms resulting from the inadvertent release of such information. Although protection of human subjects in research is of primary concern in the U.S. biomedical research system, research that uses biological materials—materials that often are distanced in time and space from the persons from whom they were obtained—raises unique challenges regarding the appropriate protection of research subjects.

Research sponsors, investigators, and Institutional Review Boards (IRBs) thus must exercise great care and sensitivity in applying professional guidelines and government regulations to protect subjects whose biological materials are used in research. Properly interpreted and modestly modified, present federal regulations can protect subjects' rights and interests and at the same time permit well-designed research to go forward using materials already in storage as well as those newly collected by investigators and others. Fundamentally, the interests of subjects and those of researchers are not in conflict. Rather, appropriate protection of subjects provides the reassurance needed if individuals are to continue to make their tissue, blood, or DNA available for research. Indeed, public confidence in the ethics and integrity of the research process translates into popular support for research in general.

Policies and guidelines governing human subjects research should permit investigators—under certain circumstances and with the informed, voluntary consent of sample sources—to have access to identifying information sufficient to enable them to gather necessary data regarding the subjects. Provided that adequate protections exist (which usually, but not always, include informed consent), such information gathering could include ongoing collection of medical records data and even requests for individuals to undergo tests to provide additional research information. In some cases, it even will be acceptable for investigators to convey information about research results to the persons whose samples have been studied. Where identifying information exists, however, a well-developed system of protections must be implemented to ensure that risks are minimized and that the interests of sample sources are protected.

Finally, any system of regulation is most likely to achieve its goals if it is as clear and as simple as possible. This is especially true in the research use of human biological materials, because the federal protections for research subjects require investigators to outline the involvement of human subjects in their studies and to undergo institutional review of their protocols. Thus, one reason to modify regulations is to clarify which protocols are subject to what sorts of prior review; likewise, illustrations and explanations may be useful in clarifying how the regulations apply to novel or complicated fields that use human biological materials.

How well does the existing Federal Policy for the Protection of Human Subjects (the so-called Common Rule, codified at 45 CFR Part 46) meet these objectives? Specifically, does it provide clear direction to research sponsors, investigators, IRBs, and others regarding the conduct of research using human biological materials in an ethical manner? NBAC finds that it does not adequately do so. In some cases, present regulatory language provides ambiguous guidance for research using human biological materials. For example, confusion about the intended meaning of terms such as "human subject," "publicly available," and "minimal risk" has stymied investigators and IRB members. Beyond these ambiguities, certain parts of current regulations are inadequate to ensure the ethical use of human biological materials in research and require some modification.

In this report, NBAC offers a series of recommendations that have been developed to address perceived difficulties in the interpretation of federal regulations and in the language of position statements of some professional organizations; ensure that research involving human biological materials will continue to benefit from appropriate oversight and IRB review, the additional burdens of which are kept to a minimum; provide investigators and IRBs with clear guidance regarding the use of human biological materials in research, particularly with regard to informed consent; provide a coherent public policy for research in this area that will endure for many years and be responsive to new developments in science;

and provide the public (including potential research subjects) with increased confidence in research that makes use of human biological materials. In particular, this report provides interpretations of several important concepts and terms in the Common Rule and recommends ways both to strengthen and clarify the regulations and to make their implementation more consistent.

Recommendations

Interpretation of the Existing Federal Regulations

NBAC offers the following recommendations to improve the interpretation and implementation of the existing federal regulations as they apply to research using human biological materials.

Recommendation 1:
Federal regulations governing human subjects research (45 CFR 46) that apply to research involving human biological materials should be interpreted by the Office for Protection from Research Risks (OPRR), other federal agencies that are signatories to the Common Rule, IRBs, investigators, and others, in the following specific ways:

a) Research conducted with unidentified samples is not human subjects research and is not regulated by the Common Rule.

b) Research conducted with unlinked samples is research on human subjects and is regulated by the Common Rule, but is eligible for exemption from IRB review pursuant to 45 CFR 46.101(b)(4).

c) Research conducted with coded or identified samples is research on human subjects and regulated by the Common Rule. It is not eligible for exemption unless the specimens or the samples are publicly available as defined by 45 CFR 46.101 (b)(4). Few collections of human biological materials are publicly available, although many are available to qualified researchers at reasonable cost. Therefore, OPRR should make clear in its guidance that in most cases this exemption does not apply to research using human biological materials.

The current federal regulations appear to make eligible for expedited review research on materials that will be collected for clinical purposes or those that will be collected in noninvasive or minimally invasive ways for research purposes. NBAC finds that there is no need to distinguish between collections originally created for clinical purposes and those created for research purposes. In both cases, research on the collected materials should be eligible for expedited review if the research presents no more than a minimal risk to the study subjects. (See the discussion of minimal risk below.)

Recommendation 2:
OPRR should revise its guidance to make clear that all minimal-risk research involving human biological materials—regardless of how they were collected—should be eligible for expedited IRB review.

Special Concerns About the Use of Unlinked Samples

Given the importance of society's interest in treating disease and developing new therapies, a policy that severely restricts research access to unidentified and unlinked samples would severely hamper research and could waste a valuable research resource. As noted in Recommendation 1, research using unlinked samples may be exempt from review. However, if coded or identified samples are rendered unlinked by the investigator, special precautions are in order.

Recommendation 3:
When an investigator proposes to create unlinked samples from coded or identified materials already under his or her control, an IRB (or other designated officials at the investigator's institution) may exempt the research from IRB review if it determines that

a) the process used to unlink the samples will be effective, and

b) the unlinking of the samples will not unnecessarily reduce the value of the research.

Requirements for Investigators Using Coded or Identified Samples

Repositories and IRBs share responsibility with investigators to ensure that research is designed and

conducted in a manner that appropriately protects human subjects from unwarranted harms.

Recommendation 4:
Before releasing coded and/or identified samples from its collection, a repository should require that the investigator requesting the samples either provide documentation from the investigator's IRB that the research will be conducted in compliance with applicable federal regulations or explain in writing why the research is not subject to those regulations.

Recommendation 5:
When reviewing and approving a protocol for research on human biological materials, IRBs should require the investigator to set forth

a) a thorough justification of the research design, including a description of procedures used to minimize risk to subjects,
b) a full description of the process by which samples will be obtained,
c) any plans to obtain access to the medical records of the subjects, and
d) a full description of the mechanisms that will be used to maximize the protection against inadvertent release of confidential information.

When an investigator obtains access to a patient's medical records, either to identify sample sources or to gather additional medical information, human subjects research is being conducted. IRBs should adopt policies to govern such research, consistent with existing OPRR guidance related to medical records research.

Obtaining Informed Consent

Research using coded or identified samples requires the consent of the source, unless the criteria for a consent waiver have been satisfied. Unfortunately, the consent obtained at the time the specimen was obtained may not always be adequate to satisfy this requirement. When research is contemplated using existing samples, the expressed wishes of the individuals who provided the materials must be respected. Where informed consent documents exist, they may indicate whether individuals wanted their sample to be used in future research and in some instances may specify the type of research.

When human biological materials are collected, whether in a research or clinical setting, it is appropriate to ask subjects for their consent to future use of their samples, even in cases where such uses are at the time unknown. In this latter case, however, particular considerations are needed to determine whether to honor prospective wishes.

Whether obtaining consent to the research use of human biological materials in a research or clinical setting, and whether the consent is new or renewed, efforts should be made to be as explicit as possible about the uses to which the material might be put and whether it is possible that the research might be conducted in such a way that the individual could be identified. Obviously, different conditions will exist for different research protocols, in different settings, and among individuals. NBAC notes that the current debate about the appropriate use of millions of stored specimens endures because of the uncertain nature of past consents. Investigators and others who collected and stored human biological materials now have the opportunity to correct past inadequacies by obtaining more specific and clearly understood informed consent.

Recommendation 6:
When informed consent to the research use of human biological materials is required, it should be obtained separately from informed consent to clinical procedures.

Recommendation 7:
The person who obtains informed consent in clinical settings should make clear to potential subjects that their refusal to consent to the research use of biological materials will in no way affect the quality of their clinical care.

Recommendation 8:
When an investigator is conducting research on coded or identified samples obtained prior to the implementation of NBAC's recommendations, general releases for research given in conjunction with a clinical or surgical procedure must not be presumed to cover all types of research over an indefinite period of time. Investigators and IRBs should review existing consent documents to determine whether the subjects anticipated and agreed to participate in the type of research proposed. If the existing documents are inadequate

and consent cannot be waived, the investigator must obtain informed consent from the subjects for the current research or in appropriate circumstances have the identifiers stripped so that samples are unlinked.

Recommendation 9:
To facilitate collection, storage, and appropriate use of human biological materials in the future, consent forms should be developed to provide potential subjects with a sufficient number of options to help them understand clearly the nature of the decision they are about to make. Such options might include, for example:

a) refusing use of their biological materials in research,
b) permitting only unidentified or unlinked use of their biological materials in research,
c) permitting coded or identified use of their biological materials for one particular study only, with no further contact permitted to ask for permission to do further studies,
d) permitting coded or identified use of their biological materials for one particular study only, with further contact permitted to ask for permission to do further studies,
e) permitting coded or identified use of their biological materials for any study relating to the condition for which the sample was originally collected, with further contact allowed to seek permission for other types of studies, or
f) permitting coded use of their biological materials for any kind of future study.*

Criteria for Waiver of Consent

When an investigator proposes to conduct research with coded or identified samples, it is considered research with human subjects. Ordinarily the potential research subject is asked whether he or she agrees to participate. Seeking this consent demonstrates respect for the person's right to choose whether to cooperate with the scientific enterprise, and it permits individuals to protect themselves against unwanted or risky invasions of privacy. But informed consent is merely one aspect of human subjects protection. It is an adjunct to—rather than a substitute for—IRB review to determine if the risks of a study are minimized and acceptable in relation to its benefits.

When a study is of minimal risk, informed consent is no longer needed by a subject as a form of self-protection against research harms. However, it is still appropriate to seek consent in order to show respect for the subject, unless it is impracticable to locate him or her in order to obtain it. Thus, when important research poses little or no risk to subjects whose consent would be difficult or impossible to obtain, it is appropriate to waive the consent requirement.

Recommendation 10:
IRBs should operate on the presumption that research on coded samples is of minimal risk to the human subject if

a) the study adequately protects the confidentiality of personally identifiable information obtained in the course of research,
b) the study does not involve the inappropriate release of information to third parties, and
c) the study design incorporates an appropriate plan for whether and how to reveal findings to the sources or their physicians should the findings merit such disclosure.

Failure to obtain informed consent may adversely affect the rights and welfare of subjects in two basic ways. First, the subject may be improperly denied the opportunity to choose whether to assume the risks that the research presents, and second, the subject may be harmed or wronged as a result of his or her involvement in research to which he or she has not consented.

Further, when state or federal law, or customary practice, gives subjects a right to refuse to have their biological materials used in research, then a consent waiver would affect their rights adversely. Medical records privacy statutes currently in place or under consideration generally allow for unconsented research use and could be interpreted to suggest a similar standard for research using human biological materials. But as new statutes are enacted, it is possible that subjects will be given explicit rights to limit access to their biological materials.

Recommendation 11:
In determining whether a waiver of consent would adversely affect subjects' rights and welfare, IRBs should be certain to consider

* Commissioners Capron, Miike, and Shapiro wrote statements regarding their concerns about various aspects of this recommendation. (See page 65 of the full report.)

a) whether the waiver would violate any state or federal statute or customary practice regarding entitlement to privacy or confidentiality,
b) whether the study will examine traits commonly considered to have political, cultural, or economic significance to the study subjects, and
c) whether the study's results might adversely affect the welfare of the subject's community.

Even when research poses no more than minimal risk and a consent waiver would not affect the rights and welfare of subjects, respect for subjects requires that their consent be sought. However, on some occasions, demonstrating this respect through consent requirements could completely halt important research. An investigator who requests a waiver of the informed consent requirement for research use of human biological materials under the current federal regulations must provide to the IRB evidence that it is not practicable to obtain consent. Unfortunately, neither the regulations nor OPRR offers any guidance on what defines practicability.

Recommendation 12:
If research using existing coded or identified human biological materials is determined to present minimal risk, IRBs may presume that it would be impracticable to meet the consent requirement (45 CFR 46.116(d)(3)). This interpretation of the regulations applies only to the use of human biological materials collected before the adoption of the recommendations contained in this report (specifically Recommendations 6 through 9 regarding informed consent). Materials collected after that point must be obtained according to the recommended informed consent process and, therefore, IRBs should apply their usual standards for the practicability requirement.

NBAC recognizes that if its recommendation that coded samples be treated as though they are identifiable is adopted, there may be an increase in the number of research protocols that will require IRB review. If, however, such protocols are then determined by an IRB to present minimal risk to a subject's rights and welfare, the requirement for consent may be waived if the practicability requirement is revised for this category of research. However, it must be noted that by dropping the requirement that consent must be obtained if practicable, NBAC does so with the expectation that the process and content of informed consent for the collection of new specimens will be explicit regarding the intentions of the subjects and the research use of their materials. (See Recommendations 6 through 9 concerning informed consent.)

According to current regulations, the fourth condition for the waiver of consent stipulates that "whenever appropriate, the subjects will be provided with additional pertinent information after participation" (45 CFR 46.116(d)(4)). Thus, according to the regulations, an IRB, while waiving consent (by finding and documenting the first three required conditions), could require that subjects be informed that they were subjects of research and that they be provided details of the study—a so-called debriefing requirement. In general, NBAC concludes that this fourth criterion for waiver of consent is not relevant to research using human biological materials and, in fact, might be harmful if it forced investigators to recontact individuals who might not have been aware that their materials were being used in research.

Recommendation 13:
OPRR should make clear to investigators and IRBs that the fourth criterion for waiver, that "whenever appropriate, the subjects will be provided with additional pertinent information after participation" (45 CFR 46.116(d)(4)), usually does not apply to research using human biological materials.

Reporting Research Results to Subjects

Experts disagree about whether findings from research should be communicated to subjects. However, most do believe that such findings should not be conveyed to subjects unless they are confirmed and reliable and constitute clinically significant or scientifically relevant information.

Recommendation 14:
IRBs should develop general guidelines for the disclosure of the results of research to subjects and require investigators to address these issues explicitly in their research plans. In general, these guidelines should reflect the presumption that the disclosure of research results to subjects represents an exceptional circumstance. Such disclosure should occur only when all of the following apply:

a) the findings are scientifically valid and confirmed,
b) the findings have significant implications for the subject's health concerns, and
c) a course of action to ameliorate or treat these concerns is readily available.

Recommendation 15:
The investigator in his or her research protocol should describe anticipated research findings and circumstances that might lead to a decision to disclose the findings to a subject, as well as a plan for how to manage such a disclosure.

Recommendation 16:
When research results are disclosed to a subject, appropriate medical advice or referral should be provided.

Considerations of Potential Harms to Others

The federal regulations governing the protection of research subjects extend only to individuals who can be identified as the sources of the biological samples. The exclusive focus of the regulations on the individual research subject is arbitrary from an ethical standpoint, because persons other than the subject can benefit or be harmed as a consequence of the research.

Recommendation 17:
Research using stored human biological materials, even when not potentially harmful to individuals from whom the samples are taken, may be potentially harmful to groups associated with the individual. To the extent such potential harms can be anticipated, investigators should to the extent possible plan their research so as to minimize such harm and should consult, when appropriate, representatives of the relevant groups regarding study design. In addition, when research on unlinked samples that poses a significant risk of group harms is otherwise eligible for exemption from IRB review, the exemption should not be granted if IRB review might help the investigator to design the study in such a way as to avoid those harms.

Recommendation 18:
If it is anticipated that a specific research protocol poses a risk to a specific group, this risk should be disclosed during any required informed consent process.

Publication and Dissemination of Research Results

Publishing research results with identifiable information in scientific or medical journals and elsewhere may pose a risk to the privacy and confidentiality of research subjects. Public disclosure of such information through written descriptions or pedigrees may cause subjects to experience adverse psychosocial effects. In addition, without the informed consent of the individual, such disclosure infringes on the rights of the subject or patient. Because of the familial nature of information in pedigrees, their publication poses particularly difficult questions regarding consent. Investigators and journal editors should be aware that the ways in which research results are publicized or disseminated could affect the privacy of human subjects. NBAC believes that the source of funding, i.e., public or private, should not be an important consideration in determining the ethical acceptability of the research.

Recommendation 19:
Investigators' plans for disseminating results of research on human biological materials should include, when appropriate, provisions to minimize the potential harms to individuals or associated groups.

Recommendation 20:
Journals should adopt the policy that the published results of research studies involving human subjects must specify whether the research was conducted in compliance with the requirements of the Common Rule. This policy should extend to all human subjects research, including studies that are privately funded or are otherwise exempt from these requirements.

Professional Education and Responsibilities

Public and professional education plays an essential role in developing and implementing effective public policy regarding use of human biological materials for research. By education, NBAC is referring not simply to the provision of information with the aim of adding to the net store of knowledge by any one person or group; rather, education refers to the ongoing effort to inform, challenge, and engage. Widespread and continuing deliberation on the subject of this report must occur to

inform and educate the public about developments in the field of genetics and other areas in the biomedical sciences, especially when they affect important cultural practices, values, and beliefs.

Recommendation 21:
The National Institutes of Health, professional societies, and health care organizations should continue and expand their efforts to train investigators about the ethical issues and regulations regarding research on human biological materials and to develop exemplary practices for resolving such issues.

Recommendation 22:
Compliance with the recommendations set forth in this report will require additional resources. All research sponsors (government, private sector enterprises, and academic institutions) should work together to make these resources available.

Use of Medical Records in Research on Human Biological Materials

In recent years, attention increasingly has been paid by policymakers to the need to protect the health information of the individual. Extensive efforts at the state and federal levels to enact such protections have resulted in the setting of a variety of limitations on access to patient medical records. NBAC notes that debates about medical privacy are relevant to researchers using human biological materials in two ways. First, these researchers often need access to patient medical records, either to identify research sample sources or to gather accompanying clinical information. Such activities constitute human subjects research and should be treated accordingly. Second, the development of statutes and regulations to protect patient medical records could have the unintended consequence of creating a dual system of protections, one for the medical record and one for human biological materials. Moreover, restrictions on access to the medical record could impede legitimate and appropriate access on the part of investigators whose protocols have undergone proper review.

Recommendation 23:
Because many of the same issues arise in the context of research on both medical records and human biological materials, when drafting medical records privacy laws, state and federal legislators should seek to harmonize rules governing both types of research. Such legislation, while seeking to protect patient confidentiality and autonomy, should also ensure that appropriate access for legitimate research purposes is maintained.

Summary

To advance human health, it is critical that human biological materials continue to be available to the biomedical research community. Increasingly, it will be essential for investigators to collect human biological materials from individuals who are willing to share important clinical information about themselves. In addition, it is crucial that the more than 282 million specimens already in storage remain accessible under appropriate conditions and with appropriate protections for the individuals who supplied this material.

The growing availability to third parties of genetic and other medical information about individuals has fueled the current debate about medical privacy and discrimination, and NBAC is sensitive to the possibility that the use of information obtained from human biological samples can lead to harms as well as benefits. These concerns require that those who agree to provide their DNA, cells, tissues, or organs for research purposes not be placed at risk. Measures to provide appropriate protections for individual privacy and for the confidentiality of clinical and research data are important if significant research is to continue. The recommendations provided in this report are intended to promote the goals of improving health through biomedical research while protecting the rights and welfare of those individuals who contribute to human knowledge through the gift of their biological materials.

Chapter 1

Overview and Introduction

The Use of Human Biological Materials in Research

Biomedical researchers have long studied human biological materials—such as cells collected in research projects, biopsy specimens obtained for diagnostic purposes, and organs and tissues removed during surgery—to increase knowledge about human diseases and to develop better means of preventing, diagnosing, and treating these diseases. Today, new technologies and advances in biology provide even more effective tools for using such resources to improve medicine's diagnostic and therapeutic potential. Human biological materials also constitute an invaluable source of information for public health planning and programming, through disease surveillance and studies of disease incidence and prevalence.

Yet, the very power of these new technologies raises a number of important ethical issues. Is it appropriate to use stored biological materials in ways that originally were not contemplated either by the people from whom the materials were collected or by those who collected the materials? Does such use harm anyone's interest? Does it matter whether the material is identified, or identifiable, as to its source, or is linked, or linkable, to other medical or personal data regarding the source?

Based on the many successes of past research that has used human biological materials, it seems highly likely that future studies also will benefit millions of people. How should this prospect be weighed against the chance that the studies could harm or wrong the individuals whose material is being studied, their families, or other groups of which they are members? Under what circumstances should researchers seek informed consent from people whose biological materials (either existing or to be collected) they propose to study? How should consent requirements be adjusted if the sources of the existing biological materials would be difficult or impossible to locate, or if they have died?

The Research Value of Human Biological Materials

The medical and scientific practice of storing human biological materials is more than 100 years old. Human biological collections—which include DNA banks, tissue banks, and repositories—vary considerably, ranging from large collections formally designated as repositories to blood or tissue informally stored in a researcher's laboratory freezer. Large collections include archived pathology materials and stored cards containing blood spots from newborn screening tests (Guthrie cards).[1] Tissue specimens are stored at military facilities, forensic DNA banks, government laboratories, diagnostic pathology and cytology laboratories, university- and hospital-based research laboratories, commercial enterprises, and nonprofit organizations.[2] Archives of human biological materials range in size from fewer than 200 specimens to more than 92 million. Conservatively estimated, at least 282 million specimens (from more than 176 million individual cases) are stored in the United States, and the collections are growing at a rate of over 20 million cases per year. (See Chapter 2.)

In this report, the term "human biological materials" is defined to encompass the full range of specimens, from subcellular structures such as DNA, to cells, tissues (e.g., blood, bone, muscle, connective tissue, and skin), organs (e.g., liver, bladder, heart, kidney, and placenta), gametes (i.e., sperm and ova), embryos, fetal tissues, and waste

(e.g., hair, nail clippings, urine, feces, and sweat, which often contains shed skin cells). At the present time, research using human embryos is not eligible for federal funding, and, therefore, current federal regulations governing research with human subjects do not apply. The use of human embryos in research does, however, raise special ethical concerns, which are addressed in part in a separate National Bioethics Advisory Commission (NBAC) report.[3] Should the congressional ban on embryo research be lifted or partially rescinded, however, many of the issues addressed in this report would be relevant to embryo research, although additional ethical considerations would apply.

The most common sources of human biological materials are diagnostic or therapeutic interventions in which diseased tissue is removed or tissue or other material is obtained to determine the nature and extent of a disease. Even after the diagnosis or treatment is complete, a portion of the specimen routinely is retained for future clinical, research, or legal purposes. Specimens also are obtained during autopsies. In addition, volunteers donate organs, blood, or other tissue for transplantation or research, and some donate their bodies after death for transplantation of organs or anatomical studies. Each specimen may be stored in multiple forms, including slides, paraffin blocks, formalin-fixed, tissue culture, or extracted DNA. Repositories provide qualified commercial and noncommercial laboratories with access to specimens for both clinical and research purposes.

In addition to its future clinical use, a specimen of human biological material can be used to study basic biology or disease. (See Chapter 2.) It can be examined to determine its normal and abnormal attributes, or it can be manipulated to develop a research tool or a potentially marketable product. Just as a clinician chooses biological materials appropriate to the clinical situation at hand, a researcher's choice of such materials depends on the goals of the research project. The selected tissue can be used only once, or it can be used to generate a renewable source of material, such as by developing a cell line, a cloned gene, or a gene marker. In addition, proteins can be extracted, or DNA isolated, from particular specimens.

There is substantial research value both in unidentified material (i.e., material that is not linked to an individual) and in material linked to an identifiable person and his or her continuing medical record. In the former, the value to the researcher of the human biological material is in the tissue itself and often in the associated clinical information about that individual, without the need to know the identity of the person from whom it came. For example, investigators may be interested in identifying a biological marker in a specific type of tissue, such as cells from individuals with Alzheimer's disease or specific tumors from a cancer patient. In such cases, beyond knowing the diagnosis of the individual from whom the specimen was obtained, researchers may not require more detailed medical records, either past or ongoing.

Sometimes, however, it is necessary to identify the source of the research sample, because the research value of the material depends upon linking findings regarding the biology of the sample with updated information from medical or other records pertaining to its source. For example, in a longitudinal study to determine the validity of a genetic marker as a predictor of certain diseases, the researchers would need to be able to link each sample with the medical record of its source in order to ascertain whether those diseases developed. In one case, a recent study of late-onset Alzheimer's disease linked the presence of the disease with the apolipoprotein-E allele by studying the stored tissues of 58 families with a history of Alzheimer's disease and then examining autopsy records for evidence of the disease in those individuals whose tissue revealed the presence of that allele (Payami et al. 1996).

Already, research using biological materials has produced tests to diagnose a predisposition to conditions such as cancer and heart disease and to a variety of genetic diseases that affect millions of individuals. In some cases, prevention or treatment is available once a diagnosis is made; in those cases, knowing the identity of the specimen source would permit communication of relevant medical information to the source that may be of importance to his or her health. In other cases, when medical interventions are unavailable, having one's specimen linked with a disease predictor is likely to be of less clinical value to the individual and might even be troubling.

Human biological materials also may be used for quality control in health care delivery, particularly in diagnostic and pathology laboratories. In addition, these

materials are used to identify an individual, such as in paternity testing and in cases of abduction or soldiers missing in action, as well as in other forensic matters for which biological evidence is available for comparison. The advent of technologies that can extract a wide array of information from these materials generally has increased the potential uses—in research and otherwise—of human biological materials that are unrelated to individual patient care.

By using the power of new DNA technologies and other molecular techniques, scientists potentially can turn to millions of stored human biological materials as sources of valuable scientific, medical, anthropological, and sociological information. Indeed, these technologies are so powerful—even revolutionary—that they also hold the ability to uncover knowledge about individuals no longer alive. Three interesting cases, reported in recent years, serve as examples:

- In 1997, scientists at the University of Oxford announced that they had compared DNA extracted from the molar cavity of a 9,000-year-old skeleton (known as Cheddar Man) to DNA collected from 20 individuals currently residing in the village of Cheddar; this resulted in the establishment of a genetic tie between the skeleton and a schoolteacher who lived just half a mile from the cave where the bones were found (DiChristina 1997).
- Scientists used enzyme-linked assays to analyze tissues more than 5,000 years old and to track the historic spread of diseases such as malaria and schistosomiasis, obtaining knowledge that can enlighten current efforts to control infectious disease.[4]
- In early 1999, a U.S. pathologist and a group of European molecular biologists announced that they had found DNA sequences in the Y chromosome of the descendants of Thomas Jefferson that matched DNA from the descendants of Sally Hemings, a slave at Monticello. The data establish only that Thomas Jefferson was the most likely of several candidates who might be the father of Eston Hemings, Hemings' fifth child, but also have raised a storm of controversy (Foster et al. 1998).

The demonstrated use of these technical capabilities suggests that human tissue and DNA specimens that have been sitting in storage banks for years—even a century—could be plumbed for new information to reveal something not only about the individual from whom the tissue was obtained, but possibly about entire groups of people who share genes, environmental exposures, and ethnic or even geographic characteristics. Clearly, the same is true for materials that may be collected in the future. DNA, whether already stored or yet to be collected, can be used to study genetic variation among people, to establish relationships between genes and characteristics (such as single gene disorders), or, more generally, to conduct basic studies of the cause and progression of disease, all with the long-term goal of improving human health. One of the many initiatives that is providing information that may help us achieve this goal is the federally funded Human Genome Project, which expects to map and sequence the entire human genome by the year 2003 (Collins et al. 1998).

Is Genetic Information Different from Other Medical Information?

In the past few decades, concern about the misuse of genetic information often has spurred debate about the misapplication of medical information in general. Public discourse and concern about the potential availability of personal genetic information has been intense in recent years for a number of reasons, including 1) the lack of any protection from the misuse of this information outside the research context (e.g., employment discrimination), 2) the role of genetic information in early and often contentious public policy debates about reproductive medicine and family planning, 3) a difficult history of and continuing concerns with relation to eugenics and genetic discrimination, and 4) the rapid pace of the Human Genome Project and other developments in human biology.

Genetic information is one form of biological or medical information. Like certain other types of medical information, genetic analyses can reveal sensitive information about an individual. Some aspects of genetic information, however, seem to many to distinguish it from other types of medical information. For example, genetic information concerning an individual sometimes can reveal similar information regarding a person's relatives or entire groups of people (ASHG 1998). In

addition, the detailed information contained in a person's genes is largely unknown to that person. Moreover, because DNA is stable, stored specimens may become the source of increasing amounts of information as new genes are mapped (Annas, Glantz, and Roche 1995). In the words of Francis Collins, Director of the National Human Genome Research Institute, "We are hurtling towards a time where individual susceptibilities will be determinable on the basis of technologies that allow your DNA sequence to be sampled and statistical predictions to be made about your future risk of illness."[5]

Some claim that the major distinguishing characteristics of genetic information are its predictive capabilities and its implications for individuals other than the person from whom the information was derived (IOM 1994). Gostin, for example, has suggested that "genomic" data are qualitatively different from other health data because they are inherently linked to one person; in other words, one's DNA is unique except in the case of identical twins (1995). In addition, genetic information does not change over time. Although other pieces of medical information about an individual might change over the course of his or her lifetime, except in the case of mutations, DNA does not.

Others argue, however, that genetic information is not inherently distinct from other types of medical information (Murray 1997). Other types of medical information may be strongly correlated with particular diseases. Moreover, infection with a virus has implications for people other than the person actually infected. Likewise, the health status of a person living in a toxic environment, such as near the Chernobyl nuclear accident site, has implications for others living in that same environment. Clearly, many of the concerns that pertain to the misuse of personal genetic information apply equally to certain other types of personal medical information.

Increasing Discussion About the Appropriate Research Use of Human Biological Materials

Increasing concerns about the use of medical information have fueled general debate about medical privacy and discrimination. Because medical research can reveal clinically relevant information about individuals, scientists must ensure that those who participate in research are protected adequately from unnecessary harms resulting from the inadvertent release of such information. Although protection of human subjects in research is of primary concern in the U.S. biomedical research system, research that uses biological materials—which are often distanced in time and space from the persons from whom they were obtained—raises unique challenges regarding the appropriate protection of research subjects. Although medical research generally is considered a public good and is supported vigorously by the American public, the power of technology to find an extraordinary amount of detailed information in a single cell raises the specter that information about individuals will be discovered and used without their consent and possibly to their detriment. Although this type of information also might be obtained through a variety of other means, DNA analysis currently is the most powerful means and increasingly is the method of choice.

In recent years, these varied concerns have resulted in consumer, scientific, and professional groups beginning to address the issues surrounding the collection and use of human biological materials (AAMC 1997; ACMG 1995; ASHG 1988; Clayton et al. 1995; Grizzle et al. 1997; HUGO 1998). In addition, media focus on highly contentious cases involving biological samples—such as the storage and research use of stored neonatal blood spots for anonymous studies of HIV prevalence in a given population and the military's establishment of a DNA bank—has made the issue of research use of human biological materials a matter of increasing public concern.

In the course of its deliberations, NBAC has identified several trends that contribute to the need for a comprehensive public policy concerning the use of these biological materials for research purposes:

- increasing public perceptions that personal genetic and other medical information could be used to discriminate against individuals in employment or by denying them access to benefits such as health or life insurance, or could be stigmatizing in some way,
- growing public concern about privacy of medical records,
- the emergence of new considerations regarding both the nature of consent to participate in research protocols and the disclosure of results, and

- disagreement among scientific and medical groups regarding conditions that need to be satisfied to ensure that appropriate ethical standards are incorporated into all research protocols using human biological materials, primarily as related to the requirements for review and to the nature of the required consent process.

One particular area of concern centers upon the question of whether the information that may be obtained from the research use of human biological materials places those who are the sources of the samples at unacceptable risk. For example, such data might reveal information about an individual's disease susceptibility (e.g., carrying a gene that is associated with an increased risk of colon cancer or breast cancer). When an intervention exists that can be pursued to counteract the increased health risk—such as regular mammograms, dietary modification, or drug treatment—some might judge the information worth receiving and worth the psychological and financial risks associated with it. If, however, the analysis reveals information about a condition for which no intervention is currently available (e.g., susceptibility to Huntington's disease or Alzheimer's disease), many individuals might perceive the risks of uncovering such information as outweighing the benefits. In any case, concern may arise when an individual did not consent in advance or show any interest in receiving such information. Some would argue that learning about an adverse health status should be intentional, since it can provoke anxiety and disrupt families, particularly if nothing can be done about it and the finding has potential implications for other family members (Wilcke 1998).

Potential for Discrimination and Stigmatization

There is growing recognition that human biological materials can be analyzed to ascertain significant amounts of genetic and other medical information about the person from whom a specimen was obtained. In particular, there is increasing concern among some policymakers and patient groups that this information could be used to discriminate against individuals in insurance and employment or could be stigmatizing for individuals and families (ASHG 1995; Hudson et al. 1995; NCHGR 1993; Rothenberg et al. 1997). In January 1998, the White House released a report entitled *Genetic Information and the Workplace*[6] that was prepared by the U.S. Departments of Labor and Health and Human Services (DHHS) and the Equal Employment Opportunity Commission. This report predicted that by the year 2000, 15 percent of employers plan to check the genetic status of prospective employees and cited a 1995 Harris poll that revealed that more than 85 percent of Americans are concerned that insurers and employers may have access to their genetic information (Taylor 1995).

Concern about insurers and employers having access to genetic information has a basis in fact. In the 1970s, several insurance companies and employers discriminated against sickle cell carriers, even though their carrier status did not and would not affect their health (Holtzman 1989). In the absence of universal access to health care or laws that prevent discrimination on the basis of health status, there is a history of concern that medical information may be used to deny individuals insurance or employment (Gostin 1991; NCHGR 1993; U.S. Congress OTA 1992). In addition to these possible financial harms, research findings about one's future medical status can, in some cases, inflict psychological or social harms (Davison, Macintyre, and Smith 1994). It should be noted, however, that to date there is little empirical evidence documenting extensive employment or insurance discrimination based on genetic status (Wertz 1997).

Concerns About Privacy of Medical Records

Health care systems increasingly rely on information technology such as electronic records to manage and facilitate the flow of sensitive and clinically relevant health information. This new reliance has had positive effects in clinical practice, but these trends also magnify concerns about privacy of certain genetic and other medical information. Recent commentary about privacy of medical records and attempts to protect privacy through legislation are evidence of the growing public concern about these issues. Currently, Congress and DHHS have been discussing legislative and regulatory approaches to protect patient privacy (U.S. Congress GAO 1999).

An ongoing concern in medical care and in the protection of research subjects is the potential invasion of privacy or the compromise of confidentiality. Measures to

provide appropriate protections, both of individual privacy and of the confidentiality of clinical and research data, are important if research using this information is to enjoy broad support. When research samples are identifiable (i.e., linked or linkable to the person who provided them), specific steps must be taken to ensure protections in the collection, storage, and use of the data. However, computerized medical records and databases raise concerns about who has access to data (i.e., the security of these databases) and about whether or not these data are linked to individual patient records. It is widely believed that current confidentiality practices are insufficient to safeguard medical information. In addition, different cultural and religious groups may have differing definitions of privacy or confidentiality (Medical Research Council 1998).

Privacy concerns may arise within the context of "secondary use" of the specimens collected. "Secondary use" means that the samples and the information derived from them are being used or analyzed for purposes that extend beyond the purpose for which the specimens were originally collected.[7] For example, when materials are collected during surgical procedures and are used solely for clinical purposes, the clinical use of these specimens raises few privacy concerns beyond those about the confidentiality of the medical record itself. This is because the materials are being used for the direct diagnostic or therapeutic benefit of an individual and because the custodian of the biological specimen does not allow others access to it. Only when the use of such materials extends beyond the original clinical use do privacy issues arise. For example, if a sample is used as part of a research study into familial linkage of a specific disease and the family pedigree is published as a result of the study, an individual might be easily identifiable even without any names attached (Botkin et al. 1998).

Body Parts, Bodies, and Self-Identity

The medical and scientific communities have become increasingly aware of a spectrum of beliefs about the relationship between a person and his or her body or body parts (Andrews and Nelkin 1998). The use of human biological materials in research can raise ethical, cultural, and religious issues about the relationships among body parts, bodies, and self-identity. However, ethical and religious traditions do not always provide clear guidance about the ways in which human tissues should be obtained or used. Although there are variations among them, selected Western religious traditions offer some insight about the significance of the human body, and they generally favor the transfer of human biological materials as "gifts." As such, human tissues would warrant some measure of respect, which is the basis often expressed for restricting sales of human tissues and organs. But cultural differences can be significant because of the different symbolic nature or status cultures attach to specific body parts or tissues.[8]

Nature of Consent to Research Participation When Human Biological Materials Are Used

Informed consent is a key component of the ethical use of persons as subjects in medical experiments. It is widely accepted and explicit in federal regulations that the informed consent of potential subjects must be obtained before enrolling them in particular research protocols. For research involving human biological materials, the role of informed consent has been much less clear, and new considerations have emerged regarding both the nature of the required consent in these cases and the guidelines that should apply regarding the disclosure of results. In particular, the use of new genetic and other technologies to study human biological materials presents several challenges to the consent process—particularly if the material is linked to a specific individual. First, because the use of the material does not pose a physical harm to the subject, potential harms become more speculative. Second, the complete research uses of the material may have been unknown and unanticipated at the time of collection. Third, the analyses might provide information that could lead to stigmatization, discrimination, or psychosocial problems for groups of individuals who share certain characteristics (Foster, Eisenbraun, and Carter 1997). Finally, there is greater awareness that the study may generate ambiguous results, tempting for clinical use but not really ready for reliable application (Reilly 1980; Reilly, Boshar, and Holtzman 1997).

In addition, physicians and hospitals customarily have not sought a patient's explicit, informed consent to permit the use of pathology specimens for specific

research purposes; instead, permission to use stored material for other than clinical purposes has been general (i.e., granted with the understanding that such use is merely a possibility). In a recent study of hospital consent forms, for example, it was found that 17 percent of large hospitals disclose potential research uses of records, and 15 percent mentioned research use of tissue samples (Merz, Sankar, and Yoo 1998). Once stored, human biological materials have been available for research, usually without the knowledge or consent of the sources, particularly if the materials are unidentifiable.

Federal regulations govern research with human subjects, including research with human biological materials. (See Appendix B, Subpart A, Part 46, Title 45 of the Code of Federal Regulations [CFR].)[9] This system of federal protections involves review of the proposed research by an Institutional Review Board (IRB) and a determination of the need for the informed consent of the research subject. In situations for which informed consent is required, the identifiability of the source of the material and the risks posed by the research are central to determining the breadth and depth of the consent requirement. (See Chapter 3 for further discussion.)

The use of human biological materials raises subtle but significant distinctions in the applicability of federal regulations, the review of research protocols, and the obtaining of consent, as the sources of materials may be patients, volunteer research subjects, or cadavers. Contention continues to surround a number of issues regarding the conditions for informed consent and/or IRB review. First, there is the question of who defines and determines what constitutes "minimal risk," an important concept in the language of the federal regulations (Merz 1996). Others believe that certain genetic research (e.g., on a stigmatizing genetic predisposition to a disease, such as alcoholism or schizophrenia) is greater than minimal risk and should, therefore, always receive a thorough IRB review. Because of these ongoing concerns, many observers, including some health advocacy and scientific groups, have called for increased attention to the consent process pertaining to the research use of stored and yet to be collected human DNA and tissues (Clayton et al. 1995).

Informed consent is a process, the effectiveness of which has been debated widely and which many agree can be improved. Discussions about its relative value in clinical and research settings are by no means unique to genetics or the issue of human biological materials. What people are told, what they understand, and what they remember when consent is sought is likely to vary as much when providing DNA or tissue as when consenting to medical interventions. When human biological material is stored, people may not understand, for example, that it might be used for research unrelated to their own disease status. When told a specimen is being kept "for research," a patient may believe the material will be used only for research related to his or her own condition. Patients may not realize that federal and state regulations require that specimens be stored for a certain length of time. In most cases, the repositories in which specimens are stored were designed for a particular purpose, and the protocols and procedures that are followed in collecting and disseminating samples might not have addressed issues regarding access, destruction, or future uses of the materials, such as for research (Merz 1996).

Other familiar issues arise with respect to informed consent. How specific, for example, must consent documents be for materials collected in a clinical context? How detailed should disclosure be regarding the intended purposes of subsequent research studies with stored materials? How much information should be provided to patients in clinical settings regarding the possibility of postdiagnostic research on stored materials? These questions are likely to have different answers depending upon whether the specimen already has been collected or will be collected in the future and upon whether the material was initially obtained as part of medical treatment or for a research protocol. It stands to reason that a person's rights and interests are better protected if that person has some form of control over his or her removed biological material, especially if it remains identifiable.

Group Concerns

Information obtained through research may have implications for families, groups, and others (Foster, Eisenbraun, and Carter 1997). Recently, the concept of community consultation in research with human subjects has received increasing attention. For example, NBAC heard testimony from the National Institute of

Allergy and Infectious Diseases (NIAID) regarding the essential nature of community involvement in NIAID's AIDS clinical trials.[10] Representatives of the community of participants in those research studies worked together with investigators in the research process, from the formulation of clinical questions to be addressed, through the design of the studies, recruitment at a community level, and the execution and analysis of the research itself. It was concluded that such participation provided invaluable benefits to the research.

The Centers for Disease Control and Prevention also has recognized the growing role of community involvement in public health initiatives, establishing a Workgroup for Community Engagement to consider a growing body of literature reflecting the experiences of those involved in engaging individuals and organizations in communities across the country (CDC 1997). While community engagement increasingly has become a basic element of health promotion, health protection, and disease prevention, few formalized procedures for seeking community involvement in research with human subjects exist.

To date, two sets of federal regulations governing informed consent procedures require a form of community consultation. The first involves research in which subjects are enrolled in studies under emergency circumstances. These regulations pertain to research subject to regulations codified by the Food and Drug Administration (FDA) and carried out under an FDA investigational new drug application or investigational device exemption (see Title 21 CFR Part 50) and research for which the Secretary of Health and Human Services has waived the general requirements for informed consent (45 CFR 46.116(a), (b), and 46.408). The regulations provide for consultation (including, when appropriate, consultation carried out by the IRB) with representatives of the communities in which the research (or clinical investigation, in the case of the FDA regulations) will be conducted and from which the subjects will be drawn. Moreover, public disclosure of plans for the research and the risks and expected benefits is required of investigators prior to initiation of the research. Finally, public disclosure of the results of the study is required following its completion. The second set of requirements has been in effect since the 1970s, and today the Indian Health Service has a policy of requiring prior to the initiation of human subjects research the approval of the Tribal Government that has legal jurisdiction (Indian Health Service 1987).

Differing Opinions Regarding the Ethical Research Use of Human Biological Materials

Recent scientific developments have increased the scientific value and importance of human biological materials. Therefore, increased demand for the use of such materials can be expected. This generates a greater level of responsibility for scientists and policymakers. From available public statements, however, it seems that the scientific community often disagrees about how to ensure the appropriate respect for persons, as well as their biological materials, while at the same time they facilitate important health and medical research. Within the past few years, many professional groups have issued policy statements describing their views on these issues. (See Appendix C.) The sheer variety of thoughtful approaches is an indication that consensus on the resolution of challenges to the use of human biological materials has been difficult to achieve, particularly with respect to requirements for IRB review and the nature of the consent process.

A stable consensus must strike the right balance between the desire to increase knowledge and the necessity of appropriately protecting individual interests. On the one hand, there are those who think that emphasis should be placed on the distinctive nature of personal and familial medical information, the right of personal choice regarding the continual use of one's body or its parts (and, therefore, the information inherent in the materials taken from it), and the necessity of being able to exercise a measure of control over the research that can be conducted with one's DNA and tissues. On the other hand, others believe that in an era of increasing professional and legal regulations as well as an increasing emphasis on individual autonomy, renewed consideration must be given to the more extensive use of this invaluable and often irreplaceable research resource; the inestimable societal and individual benefits that have been gained and that will continue to be gained through the research

use of these materials; the responsibility, explicit or implicit, of individuals to contribute to this common good, especially if risks are minimal; and the serious threat posed to the continuation of these critical research efforts by unnecessarily restrictive policies.

About This Report

In response to its original charge to consider "issues in the management and use of genetic information, including but not limited to human gene patenting," NBAC chose to first consider the research use of human biological materials, because the issue is relatively well defined, clearly important, and the focus of a great deal of current interest. There are four basic premises underlying the framework of analysis used by NBAC in the development of its recommendations:

- First, research use of human biological materials is essential to the advancement of science and human health; therefore, it is crucial that there be permissible and clearly defined conditions under which such materials can be used.
- Second, the people who provide human biological materials for research should be protected and respected.
- Third, the rapidly advancing Human Genome Project and associated technologies, as well as the application of a molecular-based approach to understanding human disease, have raised issues of autonomy and medical privacy. These issues are relevant to all areas of medical research using human biological materials, not merely genetic research.
- Fourth, there is disagreement within the scientific community about the nature of risks to individuals and about the levels and types of protections that are needed to ensure that biological samples can be used in research with minimal risks to those whose materials are used.

NBAC organized its assessment of the conditions under which research using human biological materials should be permitted around five considerations:

- whether the materials were already collected and stored, or are to be collected in the future,
- the conditions under which the materials were/are collected (e.g., clinical versus research setting),
- whether the research sample used can be linked by anyone (or any combination of people) to the source,
- whether the risks posed by the research affect individuals, communities, or both, and
- the types of protections that might be employed to protect against harms (specifically, measures to protect against invasions of privacy or discrimination, such as coding schemes, individual informed consent, community consultation, and prior review and approval by an IRB).

In reviewing these issues, NBAC relied on the existing regulatory framework governing federally sponsored research involving human subjects, 45 CFR 46 (Subpart A), or the "Common Rule." It was believed that because the large and diverse community of biomedical scientists already is familiar with these regulations and because NBAC also is charged more generally with the task of reviewing the adequacy of the federal system of protections for research involving human subjects, the Common Rule would serve as a useful framework for analysis.

Organization of This Report

To assist it in its deliberations, NBAC reviewed relevant scientific, ethical, religious, legal, and policy literature, commissioned scholarly papers on several topics relevant to its tasks, and invited members of the public and representatives of professional and consumer organizations to provide written and verbal testimony. (See Appendices E, F, and G.) In addition, NBAC posted drafts of this report on its Website (www.bioethics.gov) and solicited public comments.

To date, there has been a paucity of information concerning the acquisition, use, and storage of human biological materials. For example, no central database exists to capture information about stored materials. Thus, to assist in its review, NBAC commissioned a study to assess the magnitude and characteristics of the existing collections of human biological materials. Chapter 2 summarizes what is known about storage and use of such materials, including where they are stored, the size of collections, and the sources and uses of the materials. It also provides background on the various research uses of human biological materials and a schema for classifying the status of human biological materials according to their linkage to the sample source.

Chapter 3 summarizes the existing federal regulations governing the use of human biological samples in research. (The regulations are also presented in their entirety in Appendix B.) When NBAC began its review of the use of human biological materials in research, it was aware that a number of scientific and medical organizations had done thoughtful work on the issue. Several of these organizations have developed position statements and recommendations reflecting their efforts to work through the many ethical and policy issues that the topic raises. To gain an understanding of the range of positions that exist among organizations that have considered this subject carefully, NBAC conducted a comparative analysis of these statements as they applied to the issue of protections for the appropriate use of human biological materials in research. This analysis is found in Chapter 3, as is a description of efforts to address these issues in other countries.

NBAC believes that any set of recommendations in this area must be informed by ethical considerations. Chapter 4 reviews the central considerations for policy on the research use of biological materials. It aims to articulate in a systematic way the moral considerations that should be taken into account when developing policies about the collection, storage, and use of human biological materials. Chapter 5 synthesizes the various policy issues that emerge from the preceding chapters and offers recommendations for the future.

Finally, the Commission valued the input from members of the American public (those individuals who are not clinicians, medical researchers, or ethical experts) regarding the use of human biological materials. In addition to hearing public testimony at each of its meetings on this topic, NBAC convened seven discussion forums held across the country to obtain a sense of what Americans believe and feel about uses of such materials, about the ethical obligations of those who may learn significant health risk information from the research use of such samples, and about privacy protections. Input from all of these sources assisted the Commission as it deliberated, and findings from the forums are summarized in Appendix A.

Notes

1 Guthrie cards consist of special filter paper that contains dried blood spots from newborn babies and identifying information, such as the mother's name and address, the hospital of birth, the baby's medical record number, and the baby's doctor's name and address. The cards are used to test newborns for a variety of diseases.

2 For the purposes of this report, the term “specimen” refers to the human biological material as it is stored in the repository. The term “sample” is used to refer to the material as it is used in research. NBAC believes that this distinction becomes important when considering the applicability and adequacy of the existing federal protections for human subjects.

3 NBAC addresses issues relevant to human embryo research in a separate report, forthcoming, 1999.

4 Information on the Egyptian Mummy Tissue Bank can be found at www.mcc.ac.uk/Museum/general/mummy.htm.

5 Collins, F.S. “Perspectives.” Testimony before NBAC. October 4, 1996. Bethesda, MD.

6 The report is available at www.dol.gov/dol/_sec/public/media/reports/genetics.htm.

7 See Alpert, S., 1997, “Privacy and the Analysis of Stored Tissues.” This background paper was prepared for NBAC and is available in Volume II of this report.

8 See Campbell, C., 1997, “Research on Human Tissues: Religious Perspectives.” This background paper was prepared for NBAC and is available in Volume II of this report.

9 The Federal Policy for the Protection of Human Subjects (or “Common Rule” as it is sometimes called) was promulgated by 17 federal agencies that conduct, support, or otherwise regulate human subjects research; the Food and Drug Administration also adopted certain provisions of the Common Rule. The Federal Policy is designed to make uniform the human subjects protection system in all relevant federal departments and agencies. The Common Rule and other human subjects regulations are codified at Title 45 Part 46 of the Code of Federal Regulations, and it is the National Institutes of Health Office for Protection from Research Risks that has taken the lead within the federal government in the task of harmonizing human subjects protections across agencies.

10 Presentation by John Y. Killen, M.D., Director of the National Institute of Allergy and Infectious Diseases, Division of AIDS, to NBAC on December 9, 1997.

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2

Chapter Two

Collection, Storage, and Use of Human Biological Materials in the United States

Collections of Human Biological Materials

As part of its analysis, the National Bioethics Advisory Commission (NBAC) has sought to understand and describe the magnitude, diversity, and use of collections of human biological materials in the United States. To this end, NBAC commissioned a study to assess the size and characteristics of existing collections of these materials.[1] In addition, a study was prepared that reviewed the historical contribution of collections of human biological materials to biomedical research and to the subsequent development of new clinical studies.[2] Based largely on these studies, this chapter provides information about several characteristics of collections of human biological materials; presents a schema by which NBAC classifies human biological materials (i.e., the extent to which specimens are identifiable as they exist in the repository and as research samples in a scientific study); and describes some of the important purposes for which collections of human biological materials have been used in the past and may be used in the future.

In this report, the term "human biological materials" is defined to encompass the full range of specimens, from subcellular structures such as DNA, to cells, tissues (e.g., blood, bone, muscle, connective tissue, and skin), organs (e.g., liver, bladder, heart, kidney, and placenta), gametes (i.e., sperm and ova), embryos, fetal tissues, and waste (e.g., hair, nail clippings, urine, feces, and sweat, which often contains shed skin cells). NBAC addresses the research use of human embryos and fetal tissue in a separate report.[3]

NBAC estimates that as of 1998, more than 282 million specimens of human biological materials were stored in the United States, accumulating at a rate of more than 20 million cases per year (the term "specimen" refers to an individual quantity of material; several specimens can be obtained from one case, or individual, and several specimens can be obtained from one tissue biopsy or blood drawing).[4] (See Table 2-1.) Each specimen of human tissue may be stored in multiple forms, such as slides, paraffin blocks, formalin-fixed, frozen, tissue culture, or extracted DNA. The size and detail of collections vary considerably, ranging from formal, highly organized repositories to the storage of materials in a researcher's laboratory freezer. Individual collections of human biological materials range from fewer than 200 to more than 92 million individual quantities of material and generally fall into the following categories:

- large tissue banks, repositories, and core facilities,
- materials collected as part of longitudinal studies,
- tailored collections for research studies requiring unique tissue collections,
- pathology specimens, initially collected for clinical purposes,
- newborn screening tests accumulating in various laboratory sites,
- forensic DNA banks,[5]
- umbilical cord blood banks,
- organ banks,
- blood banks,
- sperm, ovum, and embryo banks, and
- individual investigators' collections.

Large collections of human biological materials include archived pathology specimens obtained over many years during diagnostic and surgical procedures or

at autopsy and stored cards containing blood spots from newborn screening tests (Guthrie cards) that have accumulated for a number of years. These specimens are stored at military facilities, forensic and other DNA banks,[6] government laboratories, diagnostic pathology and cytology laboratories, university- and hospital-based research laboratories, commercial enterprises, and nonprofit organizations.

Two of the largest tissue repositories in the world, the National Pathology Repository and the DNA Specimen Repository for Remains Identification, are housed within a single institution, the Armed Forces Institute of Pathology (AFIP), and together they store more than 94 million specimens. (Although the repositories supported by the National Institutes of Health [NIH] are not as large as are those of AFIP, NIH is one of the largest financial supporters of repositories, providing more than $53 million in funding in Fiscal Year 1996.) Collectively, the pathology departments at Graduate Medical Education (GME) teaching institutions constitute the largest and oldest stores of tissue specimens in the United States, with some more than 100 years old.[7] In addition, state newborn screening laboratories collectively have archives that total more than 13 million individual specimens.

Together, the AFIP National Pathology Repository, GME teaching institution pathology departments, and newborn screening laboratories contain more than 265.5 million diagnostic and therapeutic specimens from more than 170 million individuals. Overall, only a small percentage of these specimens currently are used for research, educational, or quality control purposes. The vast majority of them are stored for clinical and legal reasons (e.g., confirmatory diagnoses, malpractice actions). Most of the specimens included in these collections generally are referred to as "pathology specimens" and have been the primary source of human biological materials used in research to date. In fact, the vast majority of materials currently stored in the United States originally were collected for diagnostic or therapeutic reasons (e.g., transplantation or transfusion), with varying levels of specificity regarding future uses indicated during the informed consent process.

Blood banks, for example, collect approximately 12 million units of blood a year, but only about 20,000 to 40,000 units of blood are stored at any one time, and most of the blood collected is used for transfusions, with little used for other purposes, such as research and quality control. Organ banks do not collect the same volume of tissue as do blood banks, but they are similar in that most of the organs and tissues collected are used for transplants, with little available for research. Forensic DNA banks collect and store tissues for use in

Table 2-1. Stored Human Biological Materials in the United States

Type of Repository	Number of Cases*	Number of Specimens**	New Cases/Year
Large Tissue Banks, Repositories, and Core Facilities	>2,600,000	>96,000,000	364,825
Longitudinal Studies	>263,500	>263,500	unknown
Pathology Specimens	>160,000,000	>160,000,000	>8,000,000
Newborn Screening Laboratories	>13,500,000	>13,500,000	<10,000 to >50,000
Forensic DNA Banks	380,000	380,000	unknown
Umbilical Cord Blood Banks	18,300	18,300	unknown
Organ Banks	unknown	>75,500	>75,500
Blood Banks	unknown	~12,000,000	~12,000,000
Total	>>176,500,000	>>282,000,000	>20,000,000

*A case refers to an individual.
**Specimens refers to number of units of material derived from cases. Thus, there might be several specimens obtained from a single case (or individual).

criminal investigations, while the Department of Defense DNA Specimen Repository and some commercial DNA banks store DNA specimens for remains identification. Sperm, ovum, and embryo banks store specimens for anonymous donation or for later use by the individual source. Umbilical cord blood banks also store blood for anonymous donation and later use by families who may someday need their newborns' cord blood for medical reasons.

However, as biomedical research requires more precisely categorized samples with associated clinical data, biological materials collected specifically for research purposes increasingly are in demand. In these cases, materials are more likely to have been collected with explicit consent given to their use in research. As a result of these research needs, special repositories have been established, sometimes involving multiple partners from private industry and academia. (See Exhibit 2-A.) Furthermore, a fair number of current research efforts are engaged simultaneously in creating special collections and contributing to existing banks of human biological materials, with investigators who are conducting large, longitudinal studies collecting and banking materials from study participants over considerable periods of time. Together, these special research collections now contain more than 2.3 million samples.

Identifiability of Human Biological Materials

A key consideration in deciding whether the federal regulations apply and whether Institutional Review Board review and informed consent is required for the research use of human biological materials is the determination of whether, as defined in federal regulations, a human subject is involved in the research. This determination may be affected by the extent to which biological material can be linked to the person from whom it was obtained. The debate about research use of human biological materials has been at times complicated by the fact that the language that is used varies and often is at odds with the categories used in the applicable federal regulations. For example, previous guidelines and reports frequently categorize specimens by the identifying conditions under which they are stored in repositories (with or

Exhibit 2-A: Collaboration Between Universities and Private Industry in Creating Genetics Databases

Recent advances in computer technology and the growth of the Internet have made access to biological and medical information contained in databases increasingly more manageable for researchers. In fact, computational biology—the umbrella term for bioinformatics and medical informatics—rapidly is becoming an essential skill for biochemists, epidemiologists, molecular biologists, and physicians (Smaglik 1998). One result is that collaboration between universities and private industry has become more commonplace.

Three recent examples illustrate this trend. In April 1997, the Whitehead Institute/Massachusetts Institute of Technology Center for Genome Research formed the first "functional genomics consortium" with one pharmaceutical company, Bristol-Myers Squibb, and two biotechnology firms, Affymetrix and Millennium Pharmaceuticals, in order to discover innovative ways to gather and compare genetic data (Durso 1997). The industry participants agreed to contribute a total of $8 million per year in money and equipment to the Whitehead Institute for five years in exchange for commercial rights to any technology developed under this program (Roush 1997). Two years later, ten members of the pharmaceutical industry (Bayer, Bristol-Myers Squibb, Glaxo Wellcome, Hoechst Marion Roussel, Roche Holding, Novartis, Pfizer, Searle, SmithKline Beecham, and the Zeneca Group) and the Wellcome Trust of London announced that they have formed a consortium "to create an archive of human genetic variation" that would be available free via the Internet (Marshall 1999). The participants have agreed to spend a total of $45 million to support the mapping work of the genome centers at Washington University, the Whitehead Institute, and the Sanger Centre in England. These *single nucleotide polymorphisms* or SNPs (pronounced *snips*) are map points along the DNA sequence that it is hoped will help researchers identify variant genes that contribute to the manifestation of a particular disease (Wade 1999). Most recently, representatives from SmithKline Beecham proposed an initiative to build population genetics resources using the U.K. National Health Service, which provides comprehensive health care to 59 million people as well as valuable medical information contained in detailed patient records and archived tissue samples (Fears and Poste 1999).

without identifiers), although current federal regulations permit investigators to access stored specimens, make them anonymous by removing identifiers, and then use them in research without seeking the consent of the source. (See Chapter 3 for further discussion.)

Part of the confusion surrounding the term "identifiable," therefore, arises from the fact that people sometimes refer to the state of the information attached to the biological material in the repository (i.e., the *specimen*) and sometimes refer to the biological material and the accompanying information that is provided to the researcher (i.e., the *sample*). For example, a specimen might be identified in the repository, but no identifying information is forwarded with the research sample that is sent to the scientist. This distinction is of considerable importance because the potential for both benefit and harm is greater when the sample is directly or easily linked to the donor, placing the burden of protection in different places depending on who has access to the information (i.e., the researcher, the pathologist, or both). If samples are identifiable, the potential exists for the investigator or a third party to contact the source or act in some way that might negatively affect him or her.

NBAC has adopted the following definitions of human biological materials, depending on whether they are being stored in a repository or whether some of the material from a repository has been selected for research purposes. (See below and Table 2-2.)

Repository collections include human biological materials (i.e., *specimens*) of two types:

1. Unidentified specimens are those for which identifiable personal information was not collected or, if collected, was not maintained and cannot be retrieved by the repository.
2. Identified specimens are those that are linked to personal information in such a way that the person from whom the material was obtained could be identified by name, patient number, or other information (e.g., his or her relationship to a family member whose identity is known).

Most repositories contain identified specimens, because the vast majority of human biological materials in storage originally were collected for diagnostic or therapeutic purposes and thus included identifying information. Examples of repositories that contain identified materials include pathology laboratories and newborn screening laboratories, where specimens are collected and stored with identifying information, such as the patient's name, hospital identification number, and/or Social Security number. In addition to identifying information, clinical and demographic information often is available with these specimens. In contrast, relatively few collections of human biological materials contain unidentified specimens. Consider the following examples of repositories that store unidentified specimens:

> *A repository that collects specific blood of types such as O-positive (O^+) or AB-negative (AB^-). Donors who have these blood types are asked to contribute to the bank because they have these specific types, but the only information that is recorded about the donor when the specimen is collected is the blood type.*
>
> *A repository that collects human biological materials, such as brain, pancreas, or kidney tissues that originally were collected by a hospital, but are submitted to the repository with no identifying information. These specimens may be accompanied with some corresponding clinical and demographic information, but any information provided with the specimen is insufficient, either directly or indirectly, to identify the individual from whom the specimen originally was collected.*

Research samples are the collections of human biological materials provided to investigators by repositories. Such materials can be categorized into at least four types, which are differentiated by the amount of information that is conveyed to the investigator about the person from whom the sample material was obtained. NBAC defines the different types as follows:

1. Unidentified samples—sometimes termed "anonymous"—are those supplied by repositories to investigators from a collection of unidentified human biological specimens.
2. Unlinked samples—sometimes termed "anonymized"—are those that lack identifiers or codes that can link samples to identified specimens or particular individuals. Typically, repositories send unlinked samples from identified human biological specimens to investigators without identifiers or codes so that identifying particular individuals through the clinical or demographic information that is supplied with the sample or biological information derived from the

research would be extremely difficult for the investigator, the repository, or a third party. Unlinked samples also include those samples that are already in an investigator's possession and whose identifiers have been removed by a disinterested party.

3. Coded samples—sometimes termed "linked" or "identifiable" samples—are those supplied from identified specimens by repositories to investigators. However, these samples do not include any identifying information, such as patients' names or Social Security numbers. Rather, they are accompanied with codes. In such cases, although the repository (or its agent) retains the ability to link the research findings derived from a sample with the individual source by using the code, the investigator (or one reading a description of the research findings) would not be able to do so.
4. Identified samples are those supplied by repositories from identified specimens with personal identifiers (such as names or patient numbers) that are sufficient to allow the researcher to link directly the biological information derived from the research with the individual from whom the material was obtained.

By definition, *unidentified samples* can be obtained only from collections of unidentified materials. Because of the scarcity of truly anonymously collected human biological materials, few research samples are unidentifiable. An example of a researcher's collection of unidentified samples follows:

> *A researcher studying malaria needs O^+ blood to grow the malaria parasite. The researcher requests from a repository blood that is O^+. When the blood originally was collected, the repository labeled each vial with a number but kept no record of which unit of blood came from which donor.*

On the other hand, repository collections of identified materials may be provided to researchers as unlinked, coded, or identified samples. The use of unlinked samples in research is common. Unlinked samples are used when a one-time need for tissue and clinical/demographic information arises. Because no link is maintained between the sample and the individual from whom it came, neither the researcher nor the repository knows which sample came from which source. Therefore, the only way to obtain additional information about or another sample from a particular source would be to request additional materials from the entire group. The following is an example of such a scenario:

> *A researcher at a university is studying a mutation of a gene that may be associated with prostate cancer. The researcher needs 100 samples of prostate tumors with accompanying clinical information, such as the size of the tumor, and does not need any other information about the individuals from whom the tumors were removed. The researcher contacts the pathology department at the university and requests the samples. The pathologist pulls 100 specimens from the pathology archives, records in a separate file the medical records numbers of the selected specimens, removes any identifying information, gives each specimen a new unique identifier, and provides the samples to the researcher. No link is maintained between the samples and the individuals from whom they were obtained. This means that neither the researcher nor the pathologist knows which sample came from which patient, although the pathologist may retain a record of the group of 100 samples used.*

Another common category of samples used in research is *coded samples*. Coded samples may be used when a researcher anticipates the need to obtain additional medical information about the source, to provide information to the source, or to obtain additional samples over time. For coded samples, the identification of the individual is not provided. Instead, each sample receives a unique identifier, and the repository, for quality control or other purposes, maintains a link between the unique identifier and the identity of the individual. This link also provides the potential for one-way flow of information from the repository to the researcher and, at times, for a reverse flow of information from the researcher to the repository. Thus, coded samples could allow researchers to obtain follow-up data on treatment, recurrence, and survival and may allow researchers to communicate research findings to subjects or to their physicians. An example of the use of coded samples in research follows:

> *A researcher studying systemic lupus erythematosis (SLE) wants to know if there is a way to predict whether a patient will eventually require a kidney transplant. The researcher uses frozen serum from patients with SLE that has been coded for research purposes. During the course of this research, a unique serological marker is found that may be predictive of rapidly progressive kidney disease.*

The researcher wants to determine if there is a connection between the newly discovered marker and patients requiring a kidney transplant. Therefore, the researcher wants to receive follow-up information about each patient, particularly information relating to time until renal failure and need for dialysis and/or kidney transplant.

Identified samples are used when the research involves continual sample collection and/or clinical follow-up or when the researcher has direct contact with the research subject. With identified research samples, the investigator can go back directly to the source of the sample and request additional information. An example follows:

A researcher who is investigating the genetic causes of psoriasis identifies patients with psoriasis or psoriatic arthritis through medical records and requests samples of skin biopsies from the pathology laboratory. After the researcher completes the experiments on the skin biopsy samples, the patients and their families are contacted to further participate in the research by providing blood samples. This allows the researcher to perform linkage analysis to try to localize genes that may play a role in the development of psoriasis.

The Need to Identify the Sample Source for Research or Clinical Purposes

For research samples that are identified or coded, there are several possible reasons that an investigator may wish to go back to the source to gather additional clinical or biological information or to provide potentially valuable therapeutic information to the individual. Increasingly, genetic research requires that sufficient phenotypic (i.e., clinical) information accompany the genotypic (i.e., DNA-based) information obtained from the biological material. Thus, investigators identify those individuals of interest according to the requirements of their research protocol and then intensively investigate a smaller subset of that group. As smaller subpopulations of interest are identified, clinical investigators are likely to require more clinical information about the population being studied, which will entail the use of a mechanism for ongoing information retrieval. With coded research samples, the "trustee" of the sample retains the ability to gather more data for the investigator. With identified research samples, the investigator can request additional information directly. The possibility that the investigator, or an agent of the investigator, will contact the source (or the source's physician) for additional information should be discussed during the consent process.

Circumstances also may exist in which an investigator wants to provide information to the sample source, whether directly or indirectly. An example is an investigator who discovers new information that leads to an earlier diagnosis of a clinical condition, an effect of a previously administered therapy, or a misdiagnosis that might have important implications for the health of an individual source. Another example is the discovery of an infectious agent and its public health implications. In both cases, compelling arguments have been made supporting the investigator's duty to contact the source. In cases in which the implications of a finding are not clear (i.e., in which findings are preliminary or in which no effective

Table 2-2: Categories of Human Biological Materials

Repository Collections

Unidentified specimens: For these specimens, identifiable personal information was not collected or, if collected, was not maintained and cannot be retrieved by the repository.

Identified specimens: These specimens are linked to personal information in such a way that the person from whom the material was obtained could be identified by name, patient number, or clear pedigree location (i.e., his or her relationship to a family member whose identity is known).

Research Samples

Unidentified samples: Sometimes termed "anonymous," these samples are supplied by repositories to investigators from a collection of unidentified human biological specimens.

Unlinked samples: Sometimes termed "anonymized," these samples lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being.

Coded samples: Sometimes termed "linked" or "identifiable," these samples are supplied by repositories to investigators from identified specimens with a code rather than with personally identifying information, such as a name or Social Security number.

Identified samples: These samples are supplied by repositories from identified specimens with a personal identifier (such as a name or patient number) that would allow the researcher to link the biological information derived from the research directly to the individual from whom the material was obtained.

intervention is available), such contact is less desirable and more controversial. This is because the possibility exists that individuals could act on these findings, however tentative and conditional, in ways that might result in harm.

The Value of Human Biological Materials to Current Research

Historically, the science of pathology has led the way in the investigation of the mechanisms of disease causation by proceeding progressively from whole organs and tissues to cells, and then from the subcellular to the supramolecular and molecular manifestations of disease expression (Rosai 1997). The range of medical benefits already obtained through the use of stored biological samples is impressive. (See Exhibit 2-B.)

Biomedical research routinely relies on the availability of stored human biological materials as well as the willingness of individuals to participate in research protocols by donating blood, tissue, or DNA samples to research. Research in cancer, infectious diseases, and mental disorders is advanced by access to such materials. In addition, large, longitudinal studies that aim to study the causes of diseases in certain populations over time depend on a continuous source of biological materials for study. Some examples of the many areas of research that rely on the availability of stored human biological materials are provided below.

Cancer Research

Part of the reason that pathology specimens have served as invaluable resources for an enormous amount of cancer research is that the availability of large archives of carefully documented and clinically correlated specimens has permitted researchers to apply directly new detection technologies to existing biological materials. This is a far more rapid and less expensive approach than initiating new prospective studies for each new promising candidate gene for many of the varieties of human cancer. Conducting such studies not only would be extraordinarily costly in terms of dollars and human effort, but would require study periods of many years, or even decades.

Recent progress in elucidating the initiation and progression of cancer has been most dramatic and gratifying

Exhibit 2-B: Past Research Use of Human Biological Materials

- In 1953, autopsies of American soldiers killed in the Korean conflict revealed that atherosclerosis begins at a much earlier age than was previously thought and that blockage of arteries can be far advanced in the absence of symptoms; this research contributed to findings concerning diet and exercise that have had a major public health impact in this country, evidenced by a significant reduction in coronary artery disease (Enos, Holmes, and Beyer 1953; Enos, Beyer, and Holmes 1955; Solberg and Strong 1983; Strong 1986).
- In the late 1960s, the study of tissue samples from an unusual tumor of the vagina led to the discovery that a nonsteroidal estrogen hormone diethylstilbestrol (DES), then commonly given to women during pregnancy, is carcinogenic (Herbst and Scully 1970; Herbst, Ulfelder, and Poskanzer 1971; Herbst et al. 1974; Herbst 1981).
- Thirty years ago, a series of studies on tissue samples of precancerous lesions of the uterine cervix led to the routine use of Pap smears, which have played an important role in the early diagnosis and more successful treatment of cervical cancer (Herbst and Scully 1970; Herbst, Ulfelder, and Poskanzer 1971; Herbst et al. 1974; Herbst 1981; Younge, Hertig, and Armstrong 1949).
- Analysis of tissue from autopsies of persons in certain occupations, such as chemical manufacturing and uranium mining, has established causal links between exposure to environmental substances and certain diseases, including a cancer of the liver known as hepatic angiosarcoma and cancer of the bronchial epithelium (Creech and Johnson 1974; Dannaher, Tamburro, and Yam 1981; Falk et al. 1981; Popper et al. 1978; Regelson et al. 1968; Roth 1957).
- The analysis of autopsied lung tissue obtained from smokers played a major role in establishing that smoking causes lung cancer, that the risk of cancer increases with the duration of exposure to the chemicals contained in cigarette smoke, and that precancerous changes in the bronchial epithelium can be reversed by cessation of smoking (Auerbach et al. 1962; Auerbach, Hammond, and Garfinkel 1979; Flehinger et al. 1984; Frost et al. 1984).

in the area of colorectal cancer (Lengauer, Kinzler, and Vogelstein 1997). During the past decade, at least five specific genetic changes have been identified that seem to constitute a progressive pathway from normal to neoplastic colon tissues. Some of these revelations have been derived in subsets of patients with known hereditary forms of colorectal cancer, while others appear more generally to be present in those without known patterns of familial inheritance. At least one of these genetic changes, the inactivation of the p53 gene, is known to occur, at least at times, in the germline, while the others appear to be exclusively of somatic origin (Kinzler et al. 1991a; Kinzler et al. 1991b; Kinzler and Vogelstein 1996). Research on the role of the p53 gene was facilitated by the availability of a large human tissue repository containing various forms and stages of colorectal cancers, as well as blood specimens from the same patients. The tissue archive consisted largely of typically fixed and embedded specimens, but in addition, the scientists benefited immensely from a large collection of frozen samples (Fearon, Hamilton, and Vogelstein 1987; Fearon and Vogelstein 1990; Goelz et al. 1985; Vogelstein et al. 1988; Vogelstein et al. 1989).

Screening Human Biological Materials Archives to Track Viruses

Stored biological specimens can be valuable resources during public health emergencies, when investigators are trying to identify or track an emerging virus. For example, in 1993, healthy young people in the Four Corners area of the American Southwest began mysteriously dying from a form of pneumonia. Within months, the hantavirus was identified as the culprit. The rapid solution of this public health mystery can be attributed to many sources, including a suspicious clinician, an epidemiologist, observant Navajo elders, and two human tissue archives. One archive was that of the Centers for Disease Control and Prevention (CDC), which contained vast libraries of viruses, viral proteins, and serum specimens from around the world. The second archive held pulmonary tissues from the autopsied victims of this strange new disease. The availability of the CDC archive permitted initial serological screening tests, from which arose the first suggestion that a hantavirus might be involved. The initial screens were followed by tests of autopsy tissue specimens with specific hantavirus monoclonal antibodies, and, ultimately, the tissue samples were exposed to hantavirus genetic probes that revealed the presence and tissue distribution of viral genetic material. These molecular tools permitted identification of the local deer mouse as the host of the pathogenic hantavirus. Studies of older human autopsy tissue established that the virus was, in fact, not a new variant but a fairly old virus with a well-established symbiotic relationship with the mice in the region. To initiate human infections, this relationship must have been disturbed in some way (Wrobel 1995).

Human Tissue as a Singular Resource in Brain Research

Sometimes the use of biological materials is the only way to study certain human diseases and aspects of human disease, such as some diseases of the brain and the central nervous system. Currently, no accurate animal or tissue culture models exist for many common diseases of the human brain, including brain tumors and most of the primary neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis [ALS], or multiple sclerosis). Moreover, neurological specimens, particularly of the brain, often are inaccessible.

Until relatively recently, most brain tumor research was conducted with animal models or with cultured immortalized brain cell lines. Over the last five years, however, several studies correlating genetic alterations in human brain tumors with the degree of malignancy and prognosis have been conducted that relied on the availability of frozen samples and specially fixed samples of human brain cancers in order to assess gene amplification, gene deletions, gene mutations, and cell cycle parameters. Many insights into the pathobiology of brain tumors are emerging from these studies (Blessed, Tomlinson, and Roth 1968; Masliah et al. 1991; Raine 1997; Will et al. 1996).

Longitudinal Studies

Longitudinal studies, in which the same group of individuals is studied at intervals over a period of time, often collect large numbers of specimens that can be used for retrospective, current, or future research. Several

well-known longitudinal studies have been conducted over the years, including the Physicians' Health Study, the Nurses' Health Study, and the Framingham Heart Study.

As an example, the NIH Women's Health Initiative (WHI) is a 15-year research program, concluding in the year 2005, that focuses on the major causes of death, disability, and impaired quality of life in postmenopausal women. WHI's overall goal is to reduce coronary heart disease, breast and colorectal cancer, and osteoporosis in postmenopausal women through prevention, intervention, and risk factor identification. The study will involve more than 164,500 women of all races and socioeconomic backgrounds ages 50 to 79. The women will be enrolled in either a clinical trial or an observational study and will be followed for 8 to 12 years, during which time they will provide multiple blood samples. Participants sign a consent form that states that the collection of blood samples is for use in future research, which may include genetic research, and that participants will not be informed of any test results. Participants may refuse to have their samples used for genetic research. Participants' charts contain identifying information, including name, Social Security numbers, addresses, and telephone numbers, and they are barcoded. Blood samples are labeled with matching barcodes to link them back to the charts. All study records are kept indefinitely for analysis and follow-up.

Relying on Stored Materials for Locating Genes

The human genome has been identified as the complete set of genetic instructions that initiates the development of an individual. Although the DNA of any two individuals is roughly 99.9 percent identical, the last tenth of a percent of the DNA that is not identical is the source of considerable genetic variation. Inherited susceptibility to various diseases—which occurs when a gene fails to provide the correct instructions for a trait or function—is one small part of this diversity. Researchers look for genes by constructing finer and finer maps of known gene locations or by comparing the DNA of individuals (or, more commonly, of families) with a given disease or trait to the DNA of those who do not have that disease or trait.

The first phase of identifying a disease-related gene is the collection of diagnostic information and blood samples from an appropriate set of affected individuals and their relatives. Typically, blood samples are drawn from family members, and the blood cells are immortalized so that they can be grown continuously in the laboratory. These immortalized cells, called cell lines, then can be used to make DNA in unlimited quantities, allowing many different researchers access to this resource. The art of this collection phase lies in identifying the appropriate families.

Linkage studies are used widely to detect and locate genes that determine susceptibility to certain disorders. These studies often are based on the identification of large, densely affected families to compare the inheritance patterns of known sections of DNA (called markers) to the family's transmission of the disorder. If a known marker can be correlated with the presence or absence of the disorder, the location of the suspect gene is narrowed. Great strides in linkage analysis, including laboratory and statistical methods, are increasing the power of this method and decreasing its cost.

Linkage-disequilibrium studies in isolated populations capitalize upon the likelihood that the susceptibility genes for a particular disorder probably came from one or a few founding members. Whether the isolation of the population is geographic or cultural, there are fewer individuals in the community's original founding genealogies and therefore fewer variations of the disease genes within the population. This limited variation makes easier the search for genetic association with a disease, and the fact that the groups of markers that surround each of these susceptibility genes are likely to have the same limited variation further simplifies gene identification. (See Exhibit 2-C for a description of such a research study under way in Iceland.)

Pinpointing the likely genetic anomaly in linkage and linkage-disequilibrium studies can occur only when an investigator has narrowed the search to a fairly small region in the genome. That "small" region, however, still may be large enough to contain DNA that codes for dozens of traits, and the investigator must then choose which parts of the region to study further. Because the Human Genome Project is well on the way to identifying the location of all genes, the identification of possible susceptibility genes will become increasingly facile. Once the genes in a narrow DNA region are cataloged, each may be tested and the susceptibility gene identified.

An example of the use of DNA repositories in linkage studies is the National Institute of Mental Health's

Exhibit 2-C: Iceland's Health Records Database

A plan to construct a central database of health records in Iceland has garnered recent international attention both for its promise for human genetics research and for the ethical questions that it raises. The database, which will contain "nonpersonally identifiable health data" from the medical records of Icelandic citizens, was authorized by recent legislation passed in Iceland's Parliament (Act 1998). Like collections of human biological materials stored in the United States, the centralized bank of health records is regarded as a potentially valuable research resource. It also raises familiar ethical questions, including "What constitutes personally identifiable information?" "How can privacy be protected in the course of research?" and "How should research involving patient data be conducted in an ethically acceptable manner" (Act 1998)?[8]

The information to be included in this central database will come from a variety of sources, including health records, genealogical records, and genetic information from biological samples collected with informed consent from volunteers. The new legislation grants Decode Genetics a 12-year license to construct, operate, and receive a substantial share of the profit from the database. During that time, Decode will use the vast amounts of patient information to conduct research into the origin and nature of various diseases (Lyall 1999).

Several factors make Iceland a unique location for genetics research and its health records database a particularly valuable tool for researchers. First, Iceland's relatively homogeneous gene pool facilitates research into disease-causing mutations. In addition, Iceland's state-financed health care system maintains thorough health records, and various public and private sources maintain extensive genealogical records. When these records are combined with the data from biological samples, the database becomes a valuable tool in tracing the genetic factors of various diseases (Enserink 1998; Specter 1999). As an official of Iceland's Ministry of Health and Social Security comments, "This situation imposes on us an ethical obligation and gives us a unique opportunity to promote medical sciences" (Haraldsdottir 1999a).[9]

However, some observers believe that this database raises serious ethical questions. Discussion has centered on three issues: consent, privacy, and the commercialization of the database (Enserink 1999; Lewontin 1999; Lyall 1999). First, Iceland's new law allows information to be submitted without patient consent. All that is required is the consent of the health institutions that hold the medical records. Patients may "opt out" of participation by informing the Director General of Public Health of their wishes. Some have questioned whether this plan is appropriate in light of the potentially sensitive nature of the information (Lewontin 1999; Lyall 1999; Schwartz 1999). Approximately 10 percent of citizens are estimated to have opted out or plan to opt out of participation in the database.

Privacy is another concern. The very factors that make the database scientifically useful also might create a situation in which personal identification can be deduced from "nonpersonally identifiable data." For example, the new legislation permits Decode to process data on the health database and connect it with genealogical and "genetic data" (Act 1998).[10] Although the law stipulates that linking databases is allowed "provided that data are processed and connected in such a way that they cannot be linked to identifiable individuals," some experts have questioned how such requirements will work in practice (Act 1998). At least one privacy expert who evaluated the database says that identification would be easy to deduce (Berger 1999; Schwartz 1999). Still, it is difficult to know how to weigh the impact of such invasions of privacy in a country with a national system of medical insurance and in which most genealogical data is exempt from basic privacy laws (Specter 1999).

Finally, observers have questioned whether the plan to allow one company to own and operate the database is in the best interests of either science or of the people of Iceland. Although the law permits Iceland's Ministry of Health free access to the database, it permits access by others only so long as such access does not affect Decode's commercial interests. It remains unclear what the scope of access to the data will be in practice (Haraldsdottir 1999b). The new law, however, will not alter the current level of access to Iceland's health information. Subject to laws pertaining to the handling of personal data, others may continue to use health records for research.

A number of issues regarding the construction and operation of the database are still unresolved. These include how the existing European laws and standards regarding confidentiality of data will apply to information obtained from the database, and how much cooperation realistically can be expected from health practitioners (Duncan 1999).

The plan to construct this database comes at a time when a great deal of excitement is apparent regarding the prospects of clinical breakthroughs stemming from genetic epidemiology. Tissue banks represent valuable resources in this endeavor. As large-scale projects are proposed to create or utilize databases, and as many of the same questions about consent, privacy, and commercialization arise, it becomes even more critical to develop an ethical approach to the development of this promising research strategy.

Genetics Initiative, begun in 1989.[11] The goal of this special, large-scale initiative in molecular genetics is to collect data from a sufficient number of families to identify the genes that influence the onset of selected mental disorders. This initiative enabled the establishment of a national repository of demographic, clinical, diagnostic, and genetic data from individuals with bipolar disorder, schizophrenia, or Alzheimer's disease in order to aid researchers in identifying factors responsible for these disorders.

In association studies, the investigator hypothesizes that a specific gene or genes may influence the disorder and examines whether individuals with the disorder have a different version of the gene than individuals without it. Unlike linkage studies, which usually focus on large groups of related family members, association studies can be conducted using unrelated individuals.

Research Requiring Unique Tissue Collections

Most researchers using human biological materials have relied on specimens from pathology laboratories or existing tissue banks. However, some research studies require specialized samples—that is, samples with specific biological, clinical, or demographic characteristics. In such cases, a unique collection of materials must be created. Although these collections might have limited appeal to the broad research community, they are of great value to a small group of investigators.

Examples of the need for specialized samples are the health examination surveys conducted by CDC. Since 1960, CDC's National Center for Health Statistics has conducted seven health examination surveys of the population of the United States: the National Health Examination Surveys Cycles 1, 2, and 3; the National Health and Nutrition Examination Surveys (NHANES) I, II, and III; and the Hispanic Health and Nutrition Examination Survey (HHANES). These surveys are designed to assess periodically through interviews and direct physical examinations the health and nutritional status of children and adults in the United States. The surveys employ interviews to answer questions regarding demographics, socioeconomic status, dietary habits, and other health-related issues. Physical and dental examinations also are conducted, and these include physiologic assessments and laboratory tests. Blood samples are collected as part of the physiologic assessments and are placed in storage banks after the laboratory tests are completed.

Cumulatively, all of CDC's health examination surveys have analyzed and banked samples from more than 85,000 participants. The most recent survey, NHANES III,[12] conducted between 1988 and 1994, performed laboratory tests on approximately 29,314 people of all races, 1 year and older, from 81 counties in 26 states. Some of the 30 topics investigated in NHANES III included high blood pressure, high cholesterol, obesity, lung disease, osteoporosis, HIV/AIDS, hepatitis, diabetes, allergies, anemia, the effects of second-hand smoking, *Helicobacter pylori*, immunization status, growth and development, dietary intake, antioxidants, and nutritional blood measures. NHANES I analyzed blood and urine samples from 23,808 study participants, and NHANES II analyzed 20,322 samples. HHANES was a one-time survey conducted from 1982 to 1984 that provided data on 11,653 people of Hispanic origin.

Summary

This chapter provides examples of how human biological materials have been and continue to be invaluable resources for a wide variety of studies aimed at understanding the etiology and progression of disease and the effects of viral and environmental impacts on health, as well as for identifying genes that might be responsible for the underlying mechanisms of disease. Tremendous variability exists in the identifiability of the samples used, depending upon the source of the material and the purpose of the research. In some cases, such as the study of the hantavirus, identifying the individuals who served as the sources of the samples was not necessary. For other types of research, however, such as the studies of families with a high prevalence of mental illness in which extensive information on demographics, diagnosis, and family history is crucial, the ability to identify the source of the sample may be necessary.

Most of the specimens that are stored in repositories never will be used in research. And among those research studies that do use stored human biological materials, many will rely upon large numbers of unidentified or

unlinked research samples to investigate the basic mechanisms of health and disease or to screen samples for evidence of disease, environmental insult, or responsiveness to potential therapeutic agents. However, other studies will rely on coded or identifiable samples. In other words, an investigator might initially request samples with no linking data and later request that additional clinical data be linked to the sample. In still other cases, the research might require the investigator to be able to identify the sample source, or the sample source might even be a patient as well as a research subject of the investigator. How human biological materials are used in research and the extent to which samples can be linked to their sources are critical considerations in attempting to determine the risks to and necessary protections of the persons who serve as the sources of the materials.

Notes

1 Elisa Eiseman collected these data. Her report, "Stored Tissue Samples: An Inventory of Sources in the United States," 1997 (available in Volume II of this report) is not meant to be a comprehensive inventory; however, it does identify the major repositories or archives of stored human biological materials.

2 See Korn, D., 1998, "Contribution of the Human Tissue Archive to the Advancement of Medical Knowledge and the Public Health," a paper prepared for NBAC and available in Volume II of this report.

3 NBAC addresses certain issues relevant to human embryo and fetal tissue research in a separate report, forthcoming, 1999.

4 This estimate attempts to count both the numbers of individuals from whom stored human biological materials are derived as well as the number of specimens. For example, when a patient enters the hospital for a biopsy, the resulting tissue is accessioned in the pathology department as a single specimen. However, that single biopsy may generate several samples, including a number of slides, a paraffin block, and a frozen sample.

5 Only forensic DNA banks established according to state and federal regulations and laws are discussed in this report. The use of human biological materials in other repositories for forensic purposes also raises several ethical issues and is not addressed in this report.

6 The term "DNA bank" refers to a facility that stores extracted DNA, transformed cell lines, frozen blood or other tissue, or biological materials for future DNA analysis. Such materials are usually stored with some form of individual identification for later retrieval. DNA databanks are repositories of genetic information obtained from the analysis of DNA, sometimes referred to as "DNA profiles." The genetic information is usually stored in computerized form with individual identifiers.

7 Graduate Medical Education (GME) programs are the primary means of medical education beyond the four-year medical school training received by all physicians. Usually called residency programs, they are based in hospitals or other health care institutions, some of which do and some of which do not have formal relationships with medical schools. GME teaching institutions include medical schools; the Armed Forces hospitals; Veterans Affairs medical centers; the Public Health Service; state, county and city hospitals; nonprofit institutions; and health maintenance organizations.

8 "Personal data: all data on a personally identified or personally identifiable individual. An individual shall be counted as personally identifiable if he can be identified, directly or indirectly, especially by reference to an identity number, or one or more factors specific to his physical, physiological, mental, economic, cultural or social identity" (Act 1998).

9 According to a poll of 600 people conducted for an Icelandic daily paper, *Dagur,* 11.6 percent of Icelandic citizens have already opted out or plan to opt out of the database (www.mannvernd.is).

10 "The licensee shall be authorised to process data on the health sector database from the health data recorded there, provided that data are processed and connected in such a way that they cannot be linked to identifiable individuals. The licensee shall develop methods and protocols that meet the requirements of the Data Protection Commission in order to ensure confidentiality in connecting data from the health-sector database, from a database of genealogical data, and from a database of genetic data. With regard to linking the data on the health-sector database with other databases than those specified here, the Act on recording and handling of personal data shall apply" (Act 1998).

11 See the National Institute of Mental Health at www.nimh.gov/.

12 NHANES, www.cdc.gov/nchswww/about/major/nhanes/nhanes.htm.

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3

Chapter Three

Current Guidance on the Use of Human Biological Materials in Research

Introduction

Currently, in the United States, the infrastructure that oversees the use of human biological materials in research includes federal regulations, state statutes governing the privacy of and research use of medical records, policies developed by domestic scientific and professional societies, and guidelines developed by other countries and international organizations. When the National Bioethics Advisory Commission (NBAC) began its review of the use of human biological materials in research, it found that the work of a number of other organizations provided useful information regarding the range of positions that exist among those who have considered this subject carefully. This chapter summarizes the current existing federal regulations[1] and how the practice of Institutional Review Board (IRB) review and informed consent might be viewed when considering the ethical research use of human biological materials. (The federal regulations are reproduced in Appendix B of this report.) The chapter also provides a synopsis of the status of the debate over privacy of medical information and outlines existing policies regarding the research use of human biological materials that have been developed by scientific and medical organizations, both in the United States and internationally.

Scope of the Current Federal Regulations

The Federal Policy for the Protection of Human Subjects (45 CFR 46 or the "Common Rule," as it is sometimes called) is a set of regulations that was adopted independently by 17 federal agencies that conduct, support, or otherwise regulate human subjects research; the Food and Drug Administration (FDA) also adopted certain provisions of the Common Rule and is governed by additional regulations that apply to research on products in its regulatory purview.[2] As implied by its title, the Common Rule is designed to make uniform the human subjects protection system in all relevant federal departments and agencies. The National Institutes of Health Office for Protection from Research Risks (OPRR) has taken the lead within the federal government in working to make human subjects protections across agencies consistent.[3]

When the federal regulations are applied to research using human biological materials, a series of initial inquiries is needed to determine whether the regulations apply at all. This series of questions follows.

Does the Activity Constitute Research?

The federal regulations do not apply to exclusively clinical interventions, even if they are experimental procedures. Rather, they apply to research, defined as "a systematic investigation designed to develop or contribute to generalizable knowledge" (46.102(d)). Therefore, if the use of the materials occurs solely as a part of a clinical intervention, as might be the case in a pathology laboratory, then the federal regulations do not apply. If the use of materials has both clinical and research components, however, it might be subject to the federal regulations (see below). Thus, if a pathology laboratory saves tissue that was left over from a clinical intervention in order to conduct further, research-oriented testing, that research would be subject to the federal regulations.

Is the Research Subject to Federal Regulation?

The federal regulations apply only to research that is supported by funding from one of the federal agencies that subscribes to the Common Rule or to research that is conducted at an institution that has executed an Assurance with the federal government that research, including research not otherwise covered by the regulations, will nonetheless be governed by them. FDA regulations also apply to research on an investigational new drug, device, or biologic deemed to be involved in interstate commerce (21 CFR 130.2(a)(12) and (13) and 36 CFR 5037). For example, an investigator conducting privately funded research at a large university that has executed a Multiple Project Assurance with the federal government usually will be required to abide by the federal regulations.[4] Multiple Project Assurance agreements also include a provision that prevents researchers at an institution from bypassing federal regulations often by conducting the research off-site or with a private, unregulated company. Instead, these Assurances typically promise that researchers affiliated with the institution will abide by the federal regulations no matter where or with whom they work. Thus, research on human biological materials that is conducted using private funds and that involves investigators who are free of affiliations with institutions that have executed a Multiple Project Assurance and who are not conducting research on products subject to FDA regulation may not be subject to the federal human subjects regulations.

Does the Research Involve a "Human Subject?"

Currently, the federal regulations apply only to research involving a "human subject," defined as "a living individual about whom an investigator conducting research obtains: (a) data through intervention or interaction with the individual, or (b) identifiable private information." Specifically,

> Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects (46.102(f)(1) and (2)).

Based on this definition, it is apparent that an investigator who interacts with a person to obtain a new blood or saliva sample is conducting human subjects research, regardless of whether the investigator records any personal information about the subject.

When working with existing stores of biological materials, an investigator is defined as conducting research on a human subject when he or she obtains "identifiable private information." Section 46.102(f)(2) defines "identifiable" to mean "the identity of the subject is or may readily be ascertained by the investigator or… associated with the information." OPRR interprets "identifiable" to include samples with codes that, with the cooperation of others, could be broken in order to reveal the name of the sample source.[5] On the other hand, according to the regulations, research on samples provided to the investigator with no personal identifiers and without codes linked to personal identifiers would not be covered by the regulations, because no human subjects would be involved. This provision has been the cause of some confusion in the research community. According to the regulations, research on samples that are linked, even through a code, to personal information about the tissue source constitutes research on human subjects and is subject to the federal regulations.

For example, a researcher may be interested in performing basic work toward the development of the mapping and sequencing of the human genome. He or she might request tissue samples from a repository that has stored specimens from an entire kindred. The samples are identified by position within the kindred (e.g., "father," "daughter," "maternal aunt"), but the identity of

the family was not recorded at the time the materials were collected. Thus, even if the investigator and the repository were to attempt to recontact the tissue sources, it would not be possible, because their identities are unknown. In this scenario, according to the regulations, there would be no human subjects involved, no IRB review would be necessary, and consent from the tissue sources for new and unanticipated forms of research would not be required. If, however, means were developed to link this material to particular individuals, the use of these samples would, under federal regulations, become human subjects research.

Finally, under current federal regulations, only living individuals may be human subjects. Research involving tissues from individuals who are deceased at the time of the research is not subject to the Common Rule, regardless of whether prior informed consent was obtained. Such research, however, may be subject to the requirements of applicable state law. Of course, ethical concerns may pertain to the use of such tissues that are beyond the scope of current laws or regulations. In addition, in cases in which research using samples from deceased individuals involves identifiable private information about their living relatives, those relatives may themselves be human subjects under the federal regulations and must be afforded all of the required protections. Indeed, certain types of genetic research or research on families could pose risks for living relatives of the deceased (DeRenzo, Biesecker, and Meltzer 1997).

For example, if research were to be conducted on the autopsy material of a 30-year-old woman who died in a traffic accident, and it was inadvertently discovered and disclosed that she possessed the gene for Huntington's disease (which might not become manifest until age 50), then that woman's children automatically fall into a high-risk category for Huntington's disease. Were they to be informed of this finding, they would face the prospect of being tested for the gene as well as of coping with the psychosocial aspects of being at risk. It also is possible that they would face health insurance and employment discrimination.

Is the Research Eligible for an Exemption?

In some cases, research on human subjects is eligible to be exempted from IRB review and other regulatory requirements, such as subject consent. Work with "unlinked" samples is probably eligible for such an exemption. For example, one scenario might be that an institution called HBM Collection of America has in its collection a number of tissue specimens from kindreds. An investigator requests from the company samples from a family with achondroplasia (dwarfism). The company takes samples from Family Jones, strips all references to the family name "Jones," and supplies the samples to the investigator marked only by position within the family group, such as "father," "mother," "maternal aunt," or "son." The investigator has no way of knowing that the samples come from the Family Jones and thinks of them as unidentifiable. If the company has not maintained a record linking the samples to Family Jones, then, according to the regulations, no human subject is involved in the investigator's research on the samples and no IRB review or informed consent is required. However, if the company has maintained a record that it sent samples from Family Jones—and only Family Jones—to the investigator, then, in fact, the identity of each tissue source can be nearly or completely reconstructed by combining what the investigator knows (family position) with what the company knows (the name of the family). The federal regulations are somewhat ambiguous regarding whether this meets the regulatory definition of identifiability, although it appears that it would. Keeping in mind that one of the reasons for concern about the identifiability of the family is the possibility that research information could flow back to the sample source, this scenario appears to describe a situation in which information could be linked between the investigator and a particular member of the family (with some added difficulty if there is more than one maternal aunt or son).

Even more complex would be a scenario in which HBM Collection of America provides samples from several family groups, e.g., Family Jones, Family Smith, and Family Williams. In this situation, no individual tissue source can be determined with precision, but each individual can be identified as a member of the small group that makes up these three families. If the investigator were to discover provisionally that samples from one of the families provided by the company indicated that its

sources were at some risk of significant illness, he or she could be tempted to send this ambiguous but possibly useful information to the sources via the company's record of which families' samples are being studied. With respect to current federal regulations, however, it is not clear whether such a research protocol would be considered human subjects research. Even if it were, it probably would be eligible for an exemption.

For Research Requiring Review, What Are the IRB Requirements?

For research in which individuals who provide biological materials are identifiable and that, therefore, is subject to the federal regulations, two basic protections for human subjects generally come into play: 1) informed consent usually is required, and 2) IRB review is required to ensure an acceptable balance between risks and benefits. (See Appendix B for a description of IRBs.) There are, however, exceptions and variations that are pertinent to research using human biological materials.

The twin protections of informed consent and IRB review might not apply if the research is found to be exempt from the federal regulations. The positions of the persons who have the authority to determine if an exemption applies will vary among institutions, depending upon the particular terms of the Assurance negotiated with the government. In many cases, this individual will be the chair of the research or clinical department in which the investigator works. In others, it will be the chair or the administrator of the IRB.

The regulations state that such an exemption may be applied, for example, to "research involving the collection or study of existing 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" (46.101(4)). As noted, OPRR currently interprets this regulation to mean that investigators who conduct research with coded samples are not eligible for the exemption if there is a ready means by which the codes could be broken (including by cooperation with other individuals and institutions) and if specific research results could be linked to specific subjects.

Expedited IRB Review

For research that is not exempt from IRB review and informed consent by the subjects, opportunities nonetheless exist for streamlining the review process. Research activities that 1) present no more than minimal risk to human subjects and 2) involve only procedures listed in certain categories[6] may be reviewed by the IRB through the expedited review procedure (authorized by 45 CFR 46.110 and 21 CFR 56.110).

Federal regulations already make many forms of human biological materials collection (e.g., fingernail clippings, saliva samples, and small blood draws) eligible for expedited review (63 Fed Reg 60364, November 9, 1998). They also make research use of existing samples eligible for expedited review under some circumstances (63 Fed Reg 60364, Sec (f)(5)). However, the phrasing of the federal regulations is ambiguous with regard to existing collections that were developed in a research context.

For research on human biological materials, a key question concerning eligibility for expedited review will be whether the research poses more than a minimal risk to subjects. This assessment will depend upon the kind of information sought, the psychosocial and clinical significance of the research to the subjects, and the likelihood that the findings will be transmitted to the subjects or to anyone else who could associate the findings with the subjects.

Informed Consent Requirements

If the research is not otherwise exempt from federal regulations, all human subjects research generally requires informed consent of subjects. However, this requirement can be altered or waived if certain criteria, set forth at 45 CFR 46.116(d), are met:

1) The research involves no more than minimal risk to the subjects,
2) The waiver or alteration will not affect adversely the rights and welfare of the subjects,
3) The research could not be practicably carried out without the waiver or alteration, and
4) Whenever appropriate, the subjects will be provided with additional pertinent information following their participation.

The meaning of "minimal risk," therefore, is central to determining if a nonexempt protocol is eligible for a waiver of the consent requirements. It also is a key con-

sideration in determining whether a protocol is eligible for expedited review. In addition, the practicability of obtaining consent is an important consideration in reviewing research using human biological materials, as there may be a temporal and spatial distance between the time the material was obtained and the point at which it is used for research.

IRB Concern for Third-Party Interests

As mentioned earlier, the federal regulations are focused on living individuals, especially identifiable individuals. If identifiable, individuals almost always are entitled to be asked whether they wish to be human subjects of research. In addition, the IRB process is available to review a protocol to assess its risks and benefits to subjects. However, nowhere in this process are the concerns of third parties explicitly taken into account.

And yet, research on one individual may reveal important, even sensitive, information about others. Genetic testing on the deceased, as noted above, can yield information about living relatives. And testing on a number of otherwise unrelated individuals may yield information pertinent to many unrelated people who share salient characteristics, such as race, ethnicity, or the presence of a predisposing condition. This, in turn, could result in members of the group facing, among other things, stigmatization and discrimination in insurance and employment.

In the view of some, the strict focus of the federal regulations on the interests of the individual research subject may be problematic in the context of research with human biological materials. Ways in which third-party interests can be identified and protected where appropriate should be considered and are discussed further in Chapters 4 and 5.

Applying the Regulations to a Research Protocol: Issues for IRBs to Consider

Imagine a gene for a form of prostate cancer. Researchers may wish to screen large numbers of samples of prostate tissue currently stored in academic and commercial repositories to identify those who have markers for this hypothetical gene. Having identified this subset, investigators then may wish to examine the medical records of those men who appear to have the gene in order to identify correlations in areas such as medical history, symptomology, characteristics of the tumor, treatment choices, and outcomes. This work, in turn, may result in identifying further subsets for more refined study designed to correlate the gene with a particular type of tumor or treatment response.

Under current regulations, any link between the samples that are used by the researcher and the men from whom the materials were obtained would render the activity human subjects research. This identifiability, even if mediated by coding systems, would trigger the requirement for IRB review (at applicable institutions). The review might be eligible for expedited procedures, however, if the protocol were deemed to be of minimal risk to the subjects and fulfilled the other requirements for expedited review.

If the initial screen of all of the samples, conducted solely for the purpose of identifying which men have the gene, were conducted with unlinked samples, according to the regulations, the research could be exempt from IRB review. However, this would allow the researcher to receive only a limited amount of clinical and demographic information when the sample is sent from the repository. If the researcher chooses to use coded samples in order to obtain follow-up information or to communicate information back to the sample source, the research would be subject to IRB review, either full review or expedited review. In either case, it will be up to the IRB to determine whether the researcher would need to get consent from the source. This will depend upon whether the subject gave consent for such research at some time in the past. If not, the IRB will require consent unless it finds that consent can be waived because the research is of minimal risk and it is impracticable to go back to the source for that consent.

Research conducted using coded samples would allow for a second screen in which the subset of men whose tissues showed a marker for the gene would have their medical records examined. The same issues regarding minimal risk would apply to this screen, but a seemingly greater risk would exist that findings would develop in the course of research that might prompt investigators to consider communicating them to the sources or to their physicians. For example, if the data

strongly indicate that those with the markers respond dramatically better to one treatment than to another, investigators might wonder whether it would be best to communicate this information to a patient and/or to his physician so that the treatment can be pursued before the patient's health declines irreversibly.

At the same time, in the view of many, the tentative nature of such findings may make their communication problematic. For example, because some prostate treatments may have significant side effects, such as impotence and incontinence, and because the clinical data on the need to detect and treat slow-growing prostate cancers in older men are ambiguous, disclosure of such tentative findings may cause patients to experience great uncertainty and anxiety without the assurance of clinical benefit. It is the difficulty of understanding the meaning of minimal risk with regard to psychosocial harm (as opposed to physical harm) that makes this issue so complex and, in turn, makes the decision about eligibility for consent waivers so difficult. It is important to note, however, that disclosure of medical information also can be beneficial to the subject.

Medical and Scientific Organization Standards and Guidance

When NBAC began its review of the use of human biological materials in research, the thoughtful work on the issue done by a number of scientific and medical organizations was considered. Many such organizations have developed position statements and recommendations that reflect their efforts to work through the many ethical and policy issues that the topic raises. These position statements, although lacking the force of the federal regulations, can be influential in shaping the behavior and practices of the scientific community. NBAC conducted a comparative analysis of 14 statements as they applied to the issue of protections for the appropriate use of human biological materials in research. (See Appendix C.) In general, considerable disagreement was apparent among the statements regarding what constitutes an identifiable human subject, when informed consent should be required, and what constitutes proper consent. Confusion in the definitions, combined with vague regulatory language, has contributed to the considerable challenge that IRBs face in reviewing this type of research. For example, some groups call unidentified and unlinked samples *anonymous* materials, that is, materials that were originally collected without identifiers or are otherwise impossible to link to their sources. Others use the phrase "anonymous use" to indicate that although the materials may retain identifiers in the repository, the investigator does not have access to that information.

Many groups recommend different protections according to the degree to which samples used in a research protocol can be linked to a subject. Therefore, how a group defines identifiable information is important when considering the protections that it recommends. Some groups define "identifiable" samples as exclusively "coded" materials; others use the term "identifiable" to encompass both "coded" and "directly identified" materials (Clayton et al. 1995). The Pathologists Consensus Statement, for example, recommends that different protections be applied to research that uses archived, coded samples than to research that uses directly identified samples. The statement emphasizes the importance and feasibility of "maintaining patient identity and clinical information separate from research data through the use of coding" (Grizzle et al. 1997).

Many organizations have provided guidelines on how to address some of the difficult decisions that arise in the course of research using stored materials. These decisions include when and how to recontact individuals regarding consent for new research uses of their samples; how to judge the adequacy of previously given consent; and how to assess protocols that propose to remove identifying information from samples before using them in research[7] (ACMG 1995). In addition, a number of organizations have discussed extensively how to design a manageable informed consent process that would address the individual's concerns about the present and future uses of his or her sample and that would be comprehensible to patients and research subjects. The types of consent proposed range from general consent (consent to future, unspecified research uses of the material), to layered consent (which offers the subject the option to consent to a variety of classes of research), to specific consent for a unique designated protocol.

In some cases, the statements offer insightful discus-

sion regarding what level of consent is appropriate for the use of materials. Regarding general consent, the American Society of Human Genetics points out that in certain instances, general consent may be inappropriate, noting that "[i]t is inappropriate to ask a subject to grant blanket consent for all future unspecified genetic research projects on any disease or in any area if the samples are identifiable in those subsequent studies" (ASHG 1988). On the other hand, the Pathologists Consensus Statement notes that there may be value in requiring general consent, stating that "[t]o give a description of each and every research protocol which might be performed in the (sometimes distant) future on a patient's tissue is an unreasonable burden for the patient and the researcher" (Grizzle et al. 1997).

Several statements advocate a form of layered consent for collecting all samples in the future. The National Heart, Lung, and Blood Institute (NHLBI) provides thoughtful discussion on the content of a proposed three-tiered consent in which, as NHLBI describes it, an individual is offered the option of consenting to the current study (first level), a study with goals broadly related to the area of the original study (second level), and a study with goals unrelated to the area of the original study (third level) (NHLBI 1997).

International Perspectives on the Use of Human Biological Materials in Research

Statements addressing the ethical use of human tissues in research were issued in 1998 by the European Group of Ethics (EGE), advising the European Commission, the Human Genome Organisation (HUGO), the three major funding organizations in Canada, and the World Health Organization (WHO).[8] The EGE—a group of national ethics commissions—issued its *Opinion on Human Tissue Banking* (1998), which covers a wide variety of human tissues used for diagnostic, therapeutic, and research purposes. In contrast to the statements issued in the United States, the EGE opinion focuses primarily on regulating therapeutic uses of tissue (e.g., transplants) and stresses safety as an ethical imperative, calling for strict control of human tissue banks. It recommends a system that would protect the identity of the source while permitting the source to be traced if necessary in order to address matters regarding the safety of the donated tissue. The EGE also provides an overview of the status of legislation and ethical guidelines with regard to human tissue banking in the Member States of the European Union.

The HUGO Ethics Committee issued its *Statement on DNA Sampling: Control and Access*, which addresses several ethical issues pertinent to sample collection and sharing in genetic research (1998). Of primary importance in this statement is the source of the material, "that is, whether it was collected during routine medical care or during a specific research protocol since this affects the ambit and the choices available in the consent process." HUGO's Ethics Committee bases its specific recommendations concerning the use of stored materials in research on two factors: "1) the source of the sample, and 2) whether there was, at the time the sample was collected, 'general notification' of the institution's policy concerning future uses of samples." Of the categories of materials it defines, the Committee recommends the most stringent protection for the research use of "routine samples, obtained during medical care and stored…before notification of such a policy" (HUGO 1998).

Addressing research conducted in the future, the HUGO Ethics Committee provides recommendations regarding the choices that should be offered in the consent process. It lists the potential uses of the sample and the data that may be obtained from it as important information to include in the process and recommends that the consent process also should indicate "whether the sample and its information will: identify the person, code the identity, or anonymize the identity so that the person cannot be traced although some demographic and clinical data may be provided."

The statement from HUGO is notable for its focus on protecting the rights of family members in addition to those of individual sources. It notes as ethical prerequisites "respect for individual values, familial needs and cultural differences as well as the possibility of withdrawal of consent to participate." Reflecting this focus, it recommends that special considerations be made for access by "immediate relatives" in situations in which "there is a high risk of having or transmitting a serious disorder and prevention or treatment is available."

Finally, its call for international standardization of "ethical requirements for the control and access of DNA samples and information" is a recommendation echoed by other international groups.

In 1998, the three major funding organizations in Canada issued standards and procedures for governing research involving human subjects (Medical Research Council 1998). In a section devoted to the use of human tissue in research, the Canadian statement addresses issues of privacy and confidentiality, free and informed consent, and the use of previously collected tissues. Elsewhere in this document, other concerns raised by human genetic research, such as protecting families and biological relatives and the banking of genetic material, are discussed.

The Canadian statement distinguishes four categories of tissue: identifiable (immediately linkable to a specific individual), traceable (potentially traceable provided there is access to further information such as a patient record or a database), anonymous, and anonymized. It states that the investigator does not need to seek consent unless applicable law so requires "when collected tissue has been provided by persons who are not individually identifiable (anonymous and anonymized tissue), and where there are no potential harms to them." The statement notes that even when it is not possible to identify an individual, the "interests of biological relatives and distinct cultural groups may be adversely affected through research uses of their anonymous tissue." It requires that researchers involving families and groups in genetic research reveal potential harms to the ethics board and outlines how researchers will deal with those harms.

The WHO Human Genetics Programme in 1998 issued its *Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services*, which devotes a section to "Banked DNA." According to the document, the purpose of these proposed guidelines is "to assist policy-makers, officials, practitioners and other health workers in the Member States of WHO in ensuring that genetic information and genetic services are introduced into the broader medical practice of the nations in ethically acceptable ways." The WHO proposes that existing stored specimens "should not be subject to new rules for consent or recontact that may be established in the future," and states that, in the future, "a blanket informed consent that would allow use of a sample for genetic research in general, including future, as yet unspecified projects, appears to be the most efficient and economical approach, avoiding costly recontact before each new research project."

The WHO, in addressing the issue of samples to be collected in the future, recommends a list of issues to consider when policies are developed. These include the protection of individuals from possible discrimination, possible benefits to the individual from research findings, the possibility of multiple uses of the same sample in different and unforeseen research projects, possible sharing of biological materials among collaborators, and the advantages and disadvantages for individuals and researchers of removing all identifiers from a sample. In addition, the WHO's proposal, like that issued by HUGO, discusses the interests that biological relatives have in the control of DNA specimens. The document states that "control of DNA may be familial, not only individual" and recommends that "blood relatives may have access to stored DNA for purposes of learning their own genetic status, but not for purposes of learning the donor's status."

To summarize, these statements reveal that many of the guidelines are based on common ethical considerations, such as respect for privacy and confidentiality, respect for autonomy operationalized by a requirement of informed consent, and the noncommercialization of human biological materials. A common position seems to be emerging that a person's rights and interests are best protected if that person has some form of control over his or her removed biological material. Nonetheless, a rich diversity of positions exists on how to control access to and use of human biological materials and the data obtained from them. A greater standardization of policies with regard to the use of DNA samples certainly would facilitate future international cooperation in biomedical research.

Publication Guidelines

Publishing research findings in the peer-reviewed literature is a principal method of sharing research

information (Fienberg, Martin, and Straf 1985) and is an important goal of many researchers. As such, it represents a common gateway to information in the research process. Indeed, dissemination of new scientific knowledge has been described as an important ethical obligation (Meslin 1994). As gatekeepers in the process, journal editors set standards for the work that is accepted for publication and sometimes require compliance with ethical standards (Botkin et al. 1998). Ethical requirements are described in the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* published by the International Committee of Medical Journal Editors (1999) and have been adopted by more than 500 journals and the OPRR *Guidebook* (OPRR 1993). In light of the incentive to publish within the scientific community, publication requirements represent a potentially effective means of influencing research practices (Amdur and Biddle 1997).

Nonetheless, the question of whether publication requirements should include ethical standards is controversial (Caelleigh 1993; Snider 1997). The convenience or effectiveness of using publication as an ethical checkpoint may not be a sufficient reason for involving ethical standards as part of the publication process. However, one could argue that a responsibility on the part of journal editors to set ethical standards for publication stems from the harms that may arise from the act of publishing. In Chapter 4, NBAC argues that specific risks are associated with publishing pedigrees and other research information. These risks might be dramatically reduced if all journals adopted the Uniform Requirements.

Medical Record Protection

Many protocols that call for the research use of human biological materials also will require that information from relevant medical records accompany the tissue. Such information would, as noted, allow investigators to correlate characteristics of the tissue with characteristics of the etiology and the course of the patient's disease and the patient's response to various treatments.

The federal regulations that govern human subjects research apply to the use of medical records. Efforts to link one record with another or to link a record with an interview of the patient can be considered research under the federal definitions. If the records have any personal identifiers, then this constitutes human subjects research and requires IRB review and patient/subject consent, subject, of course, to the exceptions outlined above. Indeed, the regulations governing tissue use and medical record use basically are the same, and on a practical level, they treat tissue as simply another form of a medical record.

Currently, no federal law protects the privacy of medical records, unless the records are held by the government. Recent legislative movements, however, have sought to address this issue. The passage of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) effectively set a deadline for Congress to act to protect personal privacy. HIPAA required the Secretary of Health and Human Services, in consultation with the National Committee on Vital and Health Statistics, to make recommendations to Congress on ways to protect "individually identifiable" information and to establish penalties for wrongful disclosure of personal health information. The Secretary presented those recommendations in September 1997; Congress now has until August 1999 to enact a privacy law. If Congress fails to act, the Secretary is directed to promulgate regulations within 42 months of HIPAA enactment (i.e., by February 21, 2000) relating to the privacy of health information transmitted in connection with specified electronic transactions. On August 11, 1998, the Department of Health and Human Services (DHHS) proposed such regulations, designed to protect the electronic flow of medical data between health care providers, insurers, and clearinghouses from improper access or alteration. The proposed regulations and accompanying technical guidance require all parties that deal with electronic health information to establish responsible and appropriate safeguards, to develop security plans, to provide training for employees, to secure physical access to records, and to implement a digital signature procedure in order to verify the identities of the persons accessing medical records.

Although the 105th Congress considered several proposals regarding medical privacy, no law was passed during the 1998 session. The major patient protection bills that were considered all contained confidentiality

provisions and gave individuals the right to inspect and copy their medical records, except in special circumstances.[9] In addition, several legislative proposals focused exclusively on medical records confidentiality.[10] These bills differed in their treatment of certain issues, such as the appropriate uses of personally identifiable information, whether federal regulations should be applied to both federally and nonfederally funded researchers who use personally identifiable data, and how broad federal preemption of state laws pertaining to confidentiality should be.

With respect to research, the bills differed in both their treatment of federally and privately funded research and in their reliance on the current IRB system. Many of the bills required approval by an IRB for federally funded and nonfederally funded research.[11] One bill permitted disclosure to health researchers if such disclosure was "reviewed by a committee, board, or informal organization in accordance with confidentiality standards specifying permissible and impermissible uses of the information."[12]

Finally, the legislative initiatives generally differed on whether to establish a floor or a ceiling for federal standards. Many of these initiatives would have preempted most state laws, except those pertaining to mental health and public health activities.[13] Others would not have preempted any state laws that provide a greater level of protection for personally identifiable health information.[14] The latter position is generally consistent with the recommendations presented to Congress by DHHS.

State Laws

General statutory and common law rules lay the groundwork in many states for a claim of a violation of privacy against nonconsensual use of medical records. Indeed, nearly every state has laws or regulations that provide varying degrees of protection for information contained within medical records. Recently, states have adopted these statutes most often in the context of protecting the confidentiality of records regarding certain diseases, such as HIV, AIDS, and various mental illnesses. In most instances, these acts are aimed at preventing the use of such personal medical information by insurance companies and employers, thereby protecting the individual from discrimination and/or stigmatization. However, the variability of state law protections has been cited as a problem in and of itself.

Where statutes exist, they specifically may contemplate access to medical records for research use. California's medical records confidentiality law, for example, states that "information may be disclosed to public agencies, clinical investigators, health care research organizations, and accredited public or private nonprofit educational or health care institutions for bona fide research purposes. However, no information so disclosed shall be further disclosed by the recipient in any way which would permit identification of the patient."[15] This section exempts releases of unidentifiable medical information for bona fide research purposes from the law's general requirement of patient authorization for any release.

The California law defines medical information as "any individually identifiable information in possession of or derived from a provider of health care regarding a patient's medical history, mental or physical condition, or treatment,"[16] language that is similar to that of the Common Rule. Finally, it is interesting to note that California separately addresses disclosure of genetic test results contained in an "applicant or enrollee's medical records" by a health care service plan. The law forbids disclosure by a health care service plan of "results of a test for a genetic characteristic to any third party in a manner that identifies or provides identifying characteristics of the person to whom the test results apply, except pursuant to a written authorization."[17]

Florida and Minnesota laws also address specifically the use of medical records in research. Florida's general medical record confidentiality statute states that records "may not be furnished to, and the medical condition of a patient may not be discussed with, any person other than the patient or the patient's legal representative or other health care practitioners and providers involved in the care or treatment of the patient, except upon written authorization of the patient."[18] However, as in California, such records may be furnished without written authorization "[f]or statistical and scientific research, provided the information is abstracted in such a way as to protect the identity of the patient or provided written permission

is received from the patient or the patient's legal representative."[19]

In Minnesota,

> [a] provider, or a person who receives health records from a provider, may not release a patient's health records to a person without a signed and dated consent from the patient or the patient's legally authorized representative authorizing the release, unless the release is specifically authorized by law.…[A] consent is valid for one year or for a lesser period specified in the consent or for a different period provided by law.[20]

An exception to Minnesota's general rule is that health records "may be released to an external researcher solely for purposes of medical or scientific research." The state allows the release of health records generated before January 1, 1997, if the patient has not objected or does not elect to object after that date; in contrast, the state requires that, for health records generated on or after January 1, 1997, the provider must

- disclose in writing to patients currently being treated by the provider that health records, regardless of when generated, may be released and that the patient may object, in which case the records will not be released; and
- use reasonable efforts to obtain the patient's written general authorization that describes the release of records in item (i), which does not expire but may be revoked or limited in writing at any time by the patient or the patient's authorized representative.

Furthermore, in making a release for research purposes, the provider must make a reasonable effort to determine that

- the use or disclosure does not violate any limitations under which the record was collected;
- the use or disclosure in individually identifiable form is necessary to accomplish the research or statistical purpose for which the use or disclosure is to be made;
- the recipient has established and maintains adequate safeguards to protect the records from unauthorized disclosure, including a procedure for removal or destruction of information that identifies the patient; and
- further use or release of the records in individually identifiable form to a person other than the patient without the patient's consent is prohibited.

In addition to existing statutes, there has been a recent proliferation of state legislative initiatives addressing the use of medical information.[21] Many of these initiatives attempt to protect an individual's privacy interest by preventing the dissemination of personal information and do so by restricting the ability of those who hold medical records, such as hospital pathology laboratories, to give out information from the records and by restricting the ability of investigators to conduct such research except in certain circumstances.

According to many of the pending initiatives, when a researcher who uses human biological material requests additional information about the source of a sample, the record holder may have a legal obligation not to disclose that information. Primarily, information from medical records can be disclosed only if one of two conditions is fulfilled: either the patient (or the patient's legally authorized representative) provides a specific, written consent that information from his or her medical record can be released in the circumstances at hand, or the information that is requested and released will not permit identification of the individual. Exactly what constitutes identifying information often is not defined by the legislative initiatives, and it varies from state to state. Several proposed bills provide a civil action for negligent release of personal information without consent or for violation of the bills' confidentiality requirements.

Finally, many legislative initiatives prohibit research facilities from obtaining or retaining samples for genetic testing unless the source has given consent or the sample is used in anonymous research. A few states are considering bills that provide the sample source with greater control over the sample's uses by giving the source a legal property right to the sample and to the information that is derived from it.[22] To date, however, only one state has passed such a provision into law, and the property right it grants does not address the source's ability to profit monetarily from the sample.[23] What appears clear from the state legislative initiatives is that a perceived need exists to protect medical information, especially information that can be linked to an individual, from the

possible negative consequences of research conducted on human biological materials and personal information derived from such materials.

Courts themselves only recently have begun to recognize privacy rights with respect to individuals' medical records. Early cases viewed unauthorized disclosure as a form of breach of statutory duty, libel, malpractice, breach of trust, or breach of contract. The language in one New York case strongly condemned what it deemed a valid claim for unauthorized revelation of medical secrets: "Despite the fact that in no New York case has such a wrong been remedied, due most likely to the fact that so few physicians violate this fundamental obligation, it is time that the obligation not only be recognized but that the right of redress be recognized as well."[24] Similarly, the United States Court of Appeals for the Third Circuit tentatively recognized a form of a privacy right against the government's request for access to medical records in order to investigate alleged health hazards. The court balanced this right against seven factors: "the type of record requested, the information it does or might contain, the potential for harm in any subsequent nonconsensual disclosure, the injury from disclosure to the relationship in which the record was generated, the adequacy of safeguards to prevent unauthorized disclosure, the degree of need for access, and whether there is an express statutory mandate, articulated public policy, or other recognizable public interest militating toward access." In that case, the court held that "the public need prevailed over the claim that medical records in general were protected from discovery."[25] Of course, it is not necessarily true that all courts conducting this type of analysis would grant investigators access to medical records despite asserted privacy rights.

More recently, the Second Circuit found that an individual has a constitutional right to privacy regarding HIV status because a person's medical condition is a matter that an individual is normally entitled to keep private.[26] Again, it is unclear how this would apply in a medical research setting, but it is significant for its explicit reliance on constitutional levels of protection for one's right to keep medical information private. Finally, some state constitutions offer additional various types of privacy protection.[27]

Summary

In its deliberations, NBAC has reviewed the applicability of the existing federal regulations pertaining to research with human biological materials and has identified some notable ambiguities. First, the current regulations do not make completely clear what is meant by "identifiability" when determining whether in fact a human subject is involved in research conducted using human biological materials. Thus, confusion results regarding just how certain types of research relate to existing federal regulations and requirements (based on how closely the samples are linked to their sources and how easily those linkages can be accomplished). The issue of identifiability is further confounded by the researcher's growing ability to identify the source (even when ostensibly unidentified) because of the unique nature of the clinical information that accompanies the material when it is delivered from the repository. The confusion about identifiability has implications for the harms that may occur and the consent that may be required.

In addition, scientific and medical groups vary in how they define the identifiability of samples and the protections recommended for each category. Several of these groups have developed guidelines for IRBs and investigators to use as they confront the questions that arise when research using existing human biological materials is proposed. These guidelines contain discussion, although not explicit, regarding the mechanisms for ensuring that human biological materials are stored and/or used in such a way that the confidentiality of the source of the material is protected. Moreover, current federal regulations are silent on the topic of group or community harm. Thus, protocols that pose insignificant risks to individuals but that may implicate strong group interests do not receive special IRB attention. This has implications for groups such as kindreds or ethnic and racial subpopulations as well as collectivities of individuals who share a common trait, such as a genetic condition or disease status.

In addition, existing regulations offer insufficient guidance on the meaning of minimal risk or the nature of the subjects' rights and welfare to be protected, and they do not make clear the status of living relatives of

deceased individuals whose stored samples are used in research. This issue is addressed in Chapter 5; however, NBAC makes no new recommendations in this area. Although OPRR has indicated that these individuals may in fact be considered human subjects by virtue of their genetic relationship to the sample source, the regulations do not specify how this consideration is to be handled by IRBs. Finally, major unresolved issues remain that pertain to the ongoing access to medical records. These issues have significant implications for research using human biological materials.

Despite the fact that the current regulations appear to apply in most cases, other issues pertaining to adequate protections arise. For example, provision of informed consent is a required but insufficient protection of both the interests of the research subject and the investigator. Moreover, there may be overriding state laws that apply regarding the research use of medical records, thereby limiting the ability of researchers to gather unlimited information from individuals whose names are linked to the biological material. Chapter 4 addresses the ethical issues that should be considered when devising a strategy for the review and conduct of research using human biological materials.

Notes

1 As used in this report, the term "federal regulations" refers to the Department of Health and Human Services (DHHS) regulations contained in Part 46 of Title 45 of the Code of Federal Regulations, except where noted.

2 In addition, on February 28, 1997, the Food and Drug Administration announced a Proposed Approach to Regulation of Cellular and Tissue-Based Products [Docket Number 97N-0068], which encompasses an array of medical products derived from the human body and used for replacement, reproductive, or therapeutic purposes. The document is available at www.fda.gov/cber/gdlns/celltissue.txt.

3 The Office for Protection from Research Risks (OPRR) fulfills responsibilities set forth in the Public Health Service Act. These include: (1) Developing and monitoring, as well as exercising compliance oversight relative to: (a) HHS Regulations for the protection of human subjects in research conducted or supported by any component of the Department of Health and Human Services; and (b) PHS Policy on Humane Care and Use of Laboratory Animals involved in research conducted or supported by any component of the Public Health Service; (2) coordinating appropriate HHS regulations, policies, and procedures both within HHS and in coordination with other Departments and Agencies in the Federal Government; and establishing criteria for and negotiation of Assurances of Compliance with institutions engaged in HHS-conducted or supported research involving human subjects and those engaged in PHS-conducted or supported research using animals; (3) conducting programs of clarification and guidance for both the Federal and non-Federal sectors with respect to the involvement of humans and the use of animals in research; and directing the development and implementation of educational and instructional programs and generating educational resource materials; 4) evaluating the effectiveness of HHS policies and programs for the protection of human subjects and the humane care and use of laboratory animals; and (5) serving as liaison to Presidential, Departmental, Congressional, interagency, and non-governmental Commissions and Boards established to examine ethical issues in medicine and research and exercises leadership in identifying and addressing such ethical issues.

4 The regulations require that each covered institution engaged in the conduct of research involving human subjects provide a written assurance of compliance stating that it will comply with the requirements set forth in these regulations. The document is referred to as an Assurance. Each Assurance sets forth the commitment of the institution to employ the basic ethical principles of the *Belmont Report* and to comply with the regulations. There are several kinds of Assurance documents. If an independent investigator provides an assurance of compliance to OPRR, the document is called an Agreement.

5 Personal communication from Dr. Gary B. Ellis, Director, OPRR, April 8, 1998.

6 See 63 FR 60364-60367, November 9, 1998, for categories.

7 For example, the statement from the American College of Medical Genetics (ACMG) lists factors to be considered "in deciding whether it is appropriate to use previously collected samples without contacting the individual": "[A]re or will the samples be made anonymous?; the degree to which the burden of contacting individuals may make it impracticable to conduct research; existence and content of prior consent; and risks and benefits" (1995).

8 For a more in-depth analysis of ethical and legal policy statements on the use of DNA samples in human genetic research from governmental, nongovernmental, and professional bodies at the international, regional, and national levels see Knoppers, B., M. Hirtle, S. Lormeau, C.M. Laberge, and M. Laflamme, 1997, "Control of DNA Samples and Information." This background paper was prepared for NBAC and is available in Volume II of this report.

9 For example, S. 2330, S. 1890/H.R. 3605, S. 2416, H.R. 4250.

10 See "Health Care Personal Information Nondisclosure Act of 1998," S. 1921; "Medical Information Privacy and Security Act," S. 1368; "Consumer Protection and Medical Record Confidentiality Act of 1998," H.R. 3900; "Medical Privacy in the Age of New Technologies Act of 1997," H.R. 1815; "Fair Health Information Practices Act of 1997," H.R. 52, H.R. 1815.

11 See S. 1368, H.R. 1815.

12 H.R. 3900.

13 See S. 1921, H.R. 52, H.R. 3900.

14 S. 1368, H.R. 1815.

15 Cal. Civ. Code Ann. § 56.10(c)(7) (West 1982 and Supp. 1998).

16 Ibid. § 56.05(b).

17 Ibid. § 56.17.

18 Fla. Stat. § 455.667(5) (1997).

19 Ibid. § 455.667(5)(d).

20 Minn. Stat. § 144.335 subdivision 3a (1997).

21 See, for example, 1997 MA H.B. 2668; 1998 UT H.B. 271; 1997 NY S.B. 3286; 1997 MI H.B. 5459; 1997 FL S.B. 1850; 1997 DE S.B. 153.

22 See, for example, 1998 UT H.B. 271; 1997 MI H.B. 5459.

23 See Oregon's statute addressing an individual's rights in genetic information, ORS @ 659.715 (1997).

24 93 Misc. 2d 201 (N.Y. Sup. Ct. 1977).

25 *United States v. Westinghouse Electric Corp.*, 638 F.2d 570 (3d Cir. 1980).

26 *Doe v. City of New York*, 15 F.3d 264, 267 (2d Cir. 1994).

27 See, for example, Alaska Const. Art. I, Section 22; Ariz. Const. Art. II, Section 8; Cal. Const. Art. 1, Section 1; Fla. Const. Art. 1, Sections 12, 23; Haw. Const. Art. 1, Section 6; Ill. Const. Art. I, Section 6; La. Const. Art. I, Section 5; Mont. Const. Art. II, Section 10; S.C. Const. Art. I, Section 10; Wash. Const. Art. I, Section 7. Generally, these state constitutional provisions require that state action must have caused the violation for protections to apply (IOM 1994). California's constitutional privacy right is more explicit; it can be applied to privacy infringements by private parties. See Cal. Const. Art. 1, Section 1: *Heda v. Superior Court*, 225 Cal. app. 3d 525 (Cal. Dist. Ct. app. 1990); *Soroka v. Dayton Hudson Corp.* 1 Cal. Rptr. 2 d 77 (Cal. Ct. app. 1991).

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Chapter Four

Ethical Perspectives on the Research Use of Human Biological Materials

Introduction

For centuries, the scientific study of the human body has generated important medical information. Although current uses of human biological materials for diagnostic, therapeutic, research, and educational purposes contribute to this ongoing process of discovery, at the same time they raise a number of ethical issues for research subjects and their families, investigators, Institutional Review Boards (IRBs), and society in general (Merz 1996; Merz, Leonard, and Miller 1999). This chapter examines several of these ethical issues—many of which have surfaced in preceding chapters—and it provides the background for the National Bioethics Advisory Commission's (NBAC's) recommendations, which follow in Chapter 5.

As noted in Chapter 2, some human biological materials have been stored for decades, millions more specimens will be gathered and stored in the next year, and tens of millions more will be gathered and stored over the next decade. The individuals who are the sources of existing specimens are identifiable in some cases but not in others. Some of these specimens were gathered during clinical procedures for which informed consent was obtained, while others were not. However, even when informed consent was given for the medical procedures that produced the specimens, the individuals may not have consented to possible future research uses of the material. In many—perhaps most—cases, individuals were not aware that their specimens were being stored or had no knowledge that they might be used for various research purposes by a number of investigators.

Obtaining information by taking a medical history or by interpreting the tracings on an electrocardiogram may not have the same significance for many individuals and their family members as would biopsying a piece of tissue or drawing blood. Perhaps this is because the latter involves an element of fear of the unknown and the unfamiliar. However, many of the interests of the sources of biological materials may depend upon the additional (and yet to be determined) information that the materials could yield, such as information that would predict an individual's health. In addition, because the nucleated somatic cell contains the complete genetic code of the person from whom the specimen was taken, any cell from any part of the body could be subjected to genetic analysis (with the potential for providing vast amounts of information); thus, true anonymity does not ultimately exist. And some types of medical research, particularly genetic research, reveal information not only about the individual sources of the biological materials but also about members of their families or of groups with which they share certain characteristics. For all of these reasons, and because of deep concerns about possible misuses of genetic information (e.g., in employment and insurance discrimination) and particularly in light of past abuses of such information in the United States (Kevles and Hood 1992), widespread interest exists in ensuring that appropriate ethical constraints on the practices of gathering and storing human biological tissues that may be used for research are in place.

This chapter discusses the three principles—beneficence, respect for persons, and justice—that, since their formulation by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in its influential *Belmont Report* (1979), have provided a broad ethical framework for assessing and directing research involving human

subjects. The *Belmont Report* was intended "to provide an analytical framework [to] guide the resolution of ethical problems arising from research involving human subjects." This chapter also draws upon the ethical guidance provided by federal regulations designed to protect human research subjects, as well as upon laws, policies, and professional codes that bear on this subject. Particularly important are rules pertaining to privacy and confidentiality, which are now the subject of considerable societal debate in relation to computerized medical records and genetic research. In addition, this chapter refers to perspectives offered by bioethicists and others on the research use of human biological materials.[1] Several bioethicists have argued, for example, that excessively individualistic interpretations of the ethical principles and rules governing research involving human subjects fail to address the needs of relevant groups and communities (Emanuel and Weijer 1999).

Although NBAC in this report considers all of these sources of ethical guidance, it does not assume that they are equally authoritative or insightful. Rather, NBAC provides its own analysis of the major ethical issues and argues for specific ways in which to address the relevant moral concerns. Part of this analysis considers the extent to which research using human biological materials falls under the ethical principles and rules that ordinarily govern research with human subjects and the extent to which it is distinctive.

In making ethical judgments about the research use of human biological materials, it is not always necessary to pit the interests of future beneficiaries of current research against the interests of those who have provided the human biological materials. First, scientists share the moral (and often legal) obligation to design their experiments in such a way as to minimize possible harms and wrongs to subjects. Second, individuals often participate eagerly in research studies because they are altruistic or socially benevolent. Third, some patients may participate in research because they hope to benefit—now or in the future—from the resulting scientific and medical developments. Thus, virtually all parties to the discussion acknowledge both the value of biomedical research and the need to minimize harms and wrongs to subjects. Indeed, the challenge is not to trade off the potential health benefits from research against the protection of sources and others, but rather to find ways in which to maximize the opportunities for developing new knowledge and new treatments while, at the same time, ensuring appropriate protections from harms and wrongs. Only then will the public have the degree of trust in researchers and confidence in scientific research that is needed to facilitate important scientific breakthroughs.

Promoting Benefits and Minimizing Harms and Wrongs

According to the National Commission, "[b]eneficence… requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research" (National Commission 1979). The principle of beneficence thus encompasses not only research efforts to produce generalizable knowledge that can benefit society, but also efforts to avoid harming persons, to minimize possible harms, and to assess possible harms in relation to possible benefits. Researchers, IRBs, and others have an obligation to minimize harms and the risks of harm to research subjects.

All harms may be viewed as setbacks to interests (Feinberg 1987). But it is also necessary to identify and, whenever possible, assign weights to various interests of both individuals and groups. Rather than simply trying to present those interests in the abstract, this chapter considers them in relation to the principles, regulations, and guidelines that already identify many of the relevant harms and assigns them some weights relative to each other, sometimes by establishing certain presumptions and indicating the conditions under which those presumptions can be rebutted.

In addition to harms, at least as narrowly construed, wrongs can occur to individuals and to groups. That is, although a right, such as a right to privacy, can be violated, not every wrong, such as an unjustified breach of privacy, is in itself a harm or even causes a harm. For example, if someone enters our house and rummages through our possessions, but takes nothing and leaves everything exactly as it was so that we are not aware of what happened, it is appropriate to say that even though

no harm occurred, we were wronged because our right to privacy was violated. Thus, we may be wronged without being harmed, just as we may be harmed without being wronged. In short, an ethical framework that seeks to clarify policy in the area of human subjects research rests upon the concept of wrongs as well as the concept of harms.

NBAC's analysis begins with the assumption that the potential harms and wrongs to individuals and groups through research on human biological materials usually will not be physical harms or wrongs. Instead, they arise not from "touching" an individual (as would be the case in most clinical research interventions), but from the acquisition, use, or dissemination of information obtained from the research sample itself (i.e., the individuals who provide those materials). Such uses present a risk that a nonphysical harm or wrong may occur. Obviously, the easier it is to connect the sources of biological materials with the materials themselves and the more widely available the information linking sources and samples, the greater the concern about risks to the individuals involved. Hence, different ethical judgments may be appropriate for unidentified, unlinked, coded, and identified samples. However, it is not always ethically justifiable to use unidentified or unlinked samples rather than coded or identified samples, because some potentially beneficial research may require more information than can be provided by unidentified or unlinked samples. Furthermore, investigators sometimes may be tempted to choose unidentified or unlinked samples in order to avoid the more stringent standards and procedures required for coded or identified samples—for example, the requirement for measures to protect privacy and confidentiality.

Rules protecting privacy and confidentiality—concepts that are closely connected, although distinct—often protect individuals from unwanted and potentially harmful disclosures of information about themselves. Such rules reflect not only efforts to respect persons by authorizing them to determine the degree of access to this information that they will grant to others, but also by protecting persons from the potential harms that may result from the unauthorized disclosure of that information.

Potential Harms from Breaches of Privacy and Confidentiality

In Chapter 1, NBAC described some of the factors that may contribute to the potential for discrimination and stigmatization, in particular relating to privacy and confidentiality. Here, NBAC discusses some of the ethical foundations for addressing these concerns.

Privacy and Confidentiality

Privacy refers to a state or condition of limited access to an individual and to information about that individual. Rules of or rights to privacy enable individuals to maintain this state. Some definitions conflate the condition of privacy with a right to privacy, which refers to the individual's right to control access to him- or herself. However, it is useful to distinguish privacy as a state or condition from privacy as a right, because individuals can experience privacy without having any control over others' access to them (others may simply ignore them), and they can have a right to privacy that is not sufficient to guarantee their privacy (others may violate their right) (Beauchamp and Childress 1994).

Privacy is a multilayered concept. Anita Allen, for example, identifies four dimensions of genetic privacy: informational, decisional, physical, and proprietary (1997). She observes that while genetic privacy refers principally to informational privacy (Westin 1994), each of the other three dimensions also may be implicated in genetics. Physical privacy focuses on persons and personal spaces, decisional privacy on an individual's decision-making, and proprietary privacy on appropriation and ownership. All four dimensions may come into play in concerns about privacy in relation to human biological materials.

Individuals have an interest in avoiding the unnecessary exposure of their bodies to the view of others and in not having intimate or embarrassing facts about themselves disclosed, even if such exposure or disclosure does not threaten other of their interests. Concerns about privacy often are closely related to concerns about dignity, because in most, if not all, cultures, some modes of exposing the body in some contexts are considered undignified and demeaning, and some intimate information is considered embarrassing and even shameful.

For the most part, once biological material is removed from the body and analyzed, it is the interest in maintaining the confidentiality of any information derived from the material, rather than the interest in maintaining the privacy of the individual, that is the issue. Nevertheless, disclosure of particular information may be either a breach of informational privacy or a breach of confidentiality, depending upon who makes the disclosure. Confidentiality emerges as an issue when one person makes information available, whether through verbal communication, a physical examination, an analysis of biological materials, or some other means, to another person who pledges not to disclose it to others without authorization. When individuals grant access to their bodies for purposes of health care and research—for example, through providing biological materials for examination—they necessarily surrender some degree of privacy; however, they often wish to restrict access to any information that may emerge from that examination. Rules of confidentiality and rights to confidentiality expressed in professional codes, laws, and regulations authorize individuals to maintain confidentiality within certain limits.

In this report, confidentiality mainly concerns access to and use of information physically contained in a database, such as a medical record. People often want information about themselves to be kept in confidence, particularly when an agreement has been made or an expectation set that further access to their biological materials and to the information these materials contain will be limited appropriately. Although such confidentiality protections are provided in federal research regulations (45 CFR 46.116(a)(5)), nothing in the regulations will provide complete protection against the inadvertent disclosure of such information. In addition, rules of confidentiality rarely are considered absolute, and various exceptions are recognized. What counts as a justifiable limitation or exception to confidentiality will depend upon a complex weighing of conflicting legitimate interests (Andrews et al. 1994).

NBAC also is aware that publishing identifiable information in scientific and medical journals can pose a risk to privacy and confidentiality. Publishing personal information, whether through direct descriptions of individuals or through pedigrees, infringes upon the rights of subjects or patients if they have not provided informed consent for such publication (Botkin et al. 1998), and it may result in adverse psychosocial effects. IRBs can obtain further guidance on this issue (OPRR 1993). In addition, as noted in Chapter 3, journal editors should review the Uniform Requirements, a set of guidelines published by the International Committee of Medical Journal Editors for the acceptance and dissemination of research (ICMJE 1991).

Discrimination in Health Insurance and Employment

On July 14, 1997, President Clinton, upon releasing the report "Health Insurance in the Age of Genetics" (U.S. Department of Health and Human Services 1997), expressed his hope that American citizens would not be forced to "choose between saving their health insurance and taking tests that would save their lives."[2] The President was referring to the concern of some that useful genetic information might be misused to discriminate against them. In addition to concerns about misuse of genetic tests, some believe that being listed in a tumor registry or replying truthfully to questions about their family medical histories may be just as risky as having a positive test for a genetic disorder reported in their medical record. Given current social and institutional arrangements, persons known to have health problems or to have certain susceptibilities to diseases may in fact be at risk of discrimination in obtaining and maintaining health insurance and employment.

The actual extent of insurance and employment discrimination on genetic grounds remains a matter of speculation, because although some evidence is available on this subject (Lapham, Kozma, and Weiss 1996), most of it is derived from surveys in which individuals self-report discrimination, with little or no independent verification of the accuracy of their perceptions (Billings et al. 1992). Moreover, the risk of health insurance discrimination mainly involves policies, the issuance of which is subject to individual medical underwriting. However, many Americans who have private health insurance obtain it through employment-based, large-group policies that are not subject to such underwriting. Nevertheless, some

forms of individual underwriting may affect tens of millions of Americans (Stone 1996). Furthermore, many people obtain health insurance through self-insured employers, and this conflation of roles—the employer both pays for and administers the health insurance plan—may tempt some employers to discriminate in employment in order to reduce perceived health risks that could increase the cost of providing insurance.

Wertz has reported data obtained from surveys of 1,084 geneticists, primary care physicians, and a sample of patients receiving genetic counseling on a number of topics, including genetic discrimination (1997). These surveys revealed few instances of employment or insurance refusal. Still, the geneticists reported that approximately 550 individuals were refused employment, fired, or denied life insurance based on their genetic constitutions. In a Harris poll, commissioned by Wertz and involving 1,000 adults, 3 percent of the general public reported being refused employment or being fired, 3 percent reported being denied health insurance, and 5 percent reported being denied life insurance "because of an inherited disease or condition." Because employment discrimination can have such devastating consequences for individuals and their families, these data should be taken seriously, and follow-up studies in this area should be conducted (Wertz 1997).

The policies that would be needed to reduce the risks of discrimination in health insurance or employment vary with the magnitude (both probability and severity) of those risks, and hence with the institutional arrangements that either magnify or diminish them. For example, if blood were collected from identifiable individuals for use in a study of the basic biological mechanisms of platelet formation, one could argue that the disclosure of that information poses little, if any, risk of discrimination to the individuals who donated the blood. If, however, the same specimens were later used to determine whether trace amounts of alcohol could be found in the blood, the potential for discrimination increases. And if that blood were collected in the workplace, concerns about the potential for discrimination would become even more pronounced.

The risk of discrimination in health insurance is not an inevitable effect of the existence of information about illness or susceptibility; instead, it is a byproduct of the current structure of the U.S. insurance market, in which most health insurance is employer based, and some private insurers compete in part by attempting to avoid fully insuring sick (and therefore costly) individuals. If this particular set of institutional arrangements were modified in certain ways or were abolished, the risk of discrimination in health insurance could decrease substantially. At the same time, the case for restricting access to biological sample information in order to reduce the risk of insurance discrimination also would decrease. Clearly, such discrimination in life insurance and disability insurance can arise in any country that depends on private insurance and individual underwriting.[3] Furthermore, a lively debate exists in the United States and elsewhere about whether it is even possible to draw a line between genetic and nongenetic information in the context of any type of insurance system (Thomson 1998; Murray 1987).

It follows that in societies in which powerful institutions pose significant threats of discrimination on the basis of genetic or other medical information, greater restrictions on access to such information will be needed than in societies in which such threats are absent. If federal and state laws prohibiting insurance and employment discrimination on the basis of genetic and other medical information are passed and effectively implemented, the balance between interests that weigh in favor of more restricted access to and greater source control over biological samples, on the one hand, and those that weigh in favor of freer access and more permissive research uses of those samples, on the other hand, would shift accordingly. Therefore, it is important to remember that any policies developed now may require revision in the future.

Stigmatization

When disclosure of genetic or medical information occurs, an individual may suffer the harm of stigmatization, even if he or she is not denied insurance or employment. Stigmatization is closely related to discrimination; like discrimination, stigmatization is a form of exclusion by labeling, which often involves at least an intimation of unwholesomeness, taint, or blame. Stigmatization usually is imposed on individuals from without, through the

negative perceptions and judgments of others; however, individuals often internalize those negative attitudes. Although there is an unfortunate tendency to focus only on the stigmatization that results from being identified as having a genetic disorder, other types of illness can be equally or even more stigmatizing (e.g., sexually transmitted diseases, disfiguring conditions, and, in some cultures, cancer).

The burden of stigmatization varies among individuals and depends significantly on cultural attitudes toward disease. For example, some might find it stigmatizing to learn, as the result of participating in a research study, that they possess a genetic marker that predisposes them to psoriasis, a condition that can be disfiguring. Others might not consider this to be stigmatizing. Some consider it to be stigmatizing to be a Tay-Sachs disease carrier, because it has the potential to put their children's health at risk; however, others who have been found to be such carriers do not view the condition as stigmatizing (American Jewish Congress 1998). Stigmatization is not limited to associations between persons or groups and certain diseases; it also may occur when studies perpetuate certain stereotypes within ethnic or social groups.

Stigmatization is difficult to define and even harder to measure. For example, although the *Oxford English Reference Dictionary* defines stigma as "a mark or sign of disgrace or discredit," the reference to a physical characteristic does not capture adequately the type of moral wrong inflicted or harm caused when a person is made to feel ashamed, excluded, or blamed. Unfortunately, concern about stigmatization still exists in other areas of research, as NBAC noted in its recent report on research involving mental disorders (1998) and as others have observed (Nuffield Council on Bioethics 1998). When, in the future, science can provide more information about the nature (and universal prevalence) of genetic susceptibility to disease and can share this information with the public, the risk of stigmatization on genetic grounds may diminish. But more information will be needed. Given the difficulty in identifying and quantifying stigma, researchers and IRBs must find ways in which to address this issue in evaluating protocols that use human biological materials.

Familial Conflict and Other Psychosocial Harms

In some instances, biological information, like other medical information, may create intra-familial conflict. For example, genetic analysis of blood may reveal that a husband is not the father of a child. Or if a daughter tests positive for Huntington's disease, she reveals the genetic status of her parents and possibly her siblings, who may not want to be aware of this devastating information. In some cultures, a family learning that the prospective spouse of one of its members has a genetic disorder or a certain medical condition may attempt to prevent the marriage from occurring. Even if the beliefs underlying such actions reflect mistaken views about genetics or indefensible assumptions about responsibility for disease, these conflicts and the harms and wrongs that they can generate are quite real.

In addition, learning that a family member is, for example, a carrier for a genetic condition can force families into difficult situations—emotionally, physically, and economically. Information that an individual is at elevated risk for a disease such as cancer or may have unwittingly passed on a deleterious genetic trait to his or her offspring is sensitive. And in most cases, it should be provided to others only with the full knowledge and consent of the individual from whom the sample was obtained.

Group-Related Harms

Closely related to discrimination and stigmatization is another potential harm that individuals may suffer because of perceived links between medical information about them contained in a biological sample and what may be called their ascriptive (or group-based) identity. The harm of negative racial stereotyping, for example, is one that befalls individuals because of their ascriptive group identity. The term "ascriptive" indicates that the identity in question is assigned by others, independent of the choice of the individual thus identified. Individuals who are vulnerable to ascriptive identity harms have a special interest in avoiding situations in which information obtained from their biological samples contributes to the reinforcement of harmful stereotypes. Thus, it is

arbitrary to limit consideration of potential harms to those affecting the individual research subject, especially given the power of new biomedical research technologies to affect the lives of many.

The ascriptive identity harms that individual research subjects may suffer are harms that other members of their ascriptive group who have not contributed samples also may suffer as a consequence of the research. Research that is designed to study a group or that retrospectively implicates a group may, for example, place the group at risk of being perceived as unusually susceptible to disease. This, in turn, could result in members of the group facing, among other things, stigmatization and discrimination in insurance and employment whether or not they contributed samples to the study. At issue for both the individual research subject and the group is that the research might reveal information about them—namely, the higher probability of the occurrence of certain diseases—that places them at risk of psychosocial and other harms.

An individual whose identifiable sample reveals him or her to be especially susceptible to a disease may be at greater risk of harm than those individuals about whom such specific information does not exist. This fact sometimes justifies the additional special protections afforded the individual research subject. However, circumstances may exist in which the individual research subject faces less risk of harm than other members of a group to which he or she belongs. For example, a socially and economically well-situated research subject likely will be at less risk of suffering the effects of insurance and employment discrimination than those lacking stable employment or health insurance. Moreover, the stigmatization sometimes associated with a disease may be far more injurious to a group than to a particular individual, especially when the group is one that is already socially and politically marginalized. As research on human genetic variation increases, additional ethical concerns may arise regarding research on identified groups; such concerns are now the subject of research (Foster, Bernsten, and Carter 1998) and are a new priority for the federally funded Human Genome Project (Collins et al. 1998).

Respecting Persons Who Are Sources of Biological Materials

Treating Persons as Moral Agents

Every person has an interest in being treated as a moral agent—that is, as an individual capable of exercising choices consistent with his or her own values, preferences, commitments, and conceptions of good. Part of the moral justification for requiring informed consent in research and treatment is to ensure that patients and research subjects are treated respectfully as agents, not as passive objects to be used merely for the ends of others. More broadly, however, respecting persons is essential to a relationship of trust between them and the researchers who want to use their biological materials. Still more broadly, the respect owed to individuals in using information about them raises general concerns about the dignity with which human beings are treated—a concern recognized in the Universal Declaration on the Human Genome and Human Rights, recently adopted by the United Nations General Assembly (UNESCO 1998).

A case can be made that current practices concerning human biological materials sometimes fail to treat persons with due respect, because researchers may unintentionally be misleading regarding why materials are being gathered and the uses to which the materials will be put. For example, the person who draws the blood may not know that it will be stored indefinitely and may be used in any number of ways in the future, and therefore, this person may have no intention to mislead. Nevertheless, the institutionalized practice of storing biological specimens for future uses is one for which those who control the practice are responsible, and this practice, as we have seen, apparently does not always adequately inform individuals about future uses of the materials.

Informed Consent

A number of fundamental ethical questions are raised by the research use of human biological materials: What kind of consent is needed for research use? Who should provide this consent? For what purpose should the consent be provided? Informed consent is recognized to be both a legal and moral requirement for medical interventions in general and for all experiments with human

subjects that involve more than minimal risk. In addition to the review of research involving human subjects by an IRB, informed consent has been a primary, albeit imperfect, means for protecting the interests, welfare, and rights of individuals who are subjects of research.

As this chapter has indicated, risks encompass not only potential physical harms from bodily invasions, including the minimal harms that may result from procedures such as drawing blood or swabbing cells from the inside of a cheek, but also psychosocial harms, especially stigmatization and other assaults on an individual's sense of self-worth. In other words, when people allow others access to their bodies, they become vulnerable to other unwanted and potentially more serious harms. For this reason, it is misleading to suggest that informed consent protects a person who is undergoing a simple procedure such as giving blood only from the remote possibility of harm that may result from the needle stick (beyond the unpleasant but momentary sensation of the needle stick itself).

Five elements of informed consent can be distinguished: 1) disclosure (of relevant risks and benefits of the procedure), 2) competence (on the part of the patient or subject) to make a decision whether to accept the treatment or to participate in the research, 3) comprehension (of the relevant risks and benefits), 4) choice (an expressed decision to accept the treatment or participate in the experimentation), and 5) voluntariness (of the choice to accept treatment or to participate in research) (Faden and Beauchamp 1986). Clearly, informed consent plays a role in any ethically sound system for collecting and using biological samples, at least to this extent: The requirement of informed consent must be met for medical treatments in general and for most types of research. The question is whether an ethically sound system for collecting, storing, and using biological samples will require additional or amplified applications of the requirement of informed consent in order to express all that the principle of respect for persons entails in this context. In Chapter 5, NBAC offers several recommendations for specifying the requirements of the principle of respect for persons, for specifying the rule of informed consent for this specific context, and for reducing the risks of various wrongs and harms that are discussed in this chapter.

It is one thing to argue that the prevention of nonconsensual bodily invasion and disrespectful treatment justifies restrictions on research, and quite another to argue that the mere possibility of various wrongs and harms—some of which may not be so serious and others of which may be unlikely to occur—provides an equally compelling reason to restrict research. Informed consent clearly is required when risks are more than minimal in order to allow the individual to decide whether the potential harms are relevant and substantial. Yet, some of the harms mentioned in this chapter are not certain, and in many cases they are extremely unlikely. Therefore, in such cases, consideration may be given to waiving the requirement for informed consent.

Special issues arise in interpreting the requirements of the principle of respect for persons and the rule of informed consent in research in the context of using existing biological materials for research purposes. As noted earlier, hundreds of thousands and perhaps millions of individual specimens may have been collected as part of clinical procedures, without patients' providing specific consent to their use in research. Thus, existing collections present a special challenge, given the value that federal (and, indeed, international) regulations, guidelines, and codes place on informed consent. The ethical question is whether biological materials that are collected without consent—or without specific consent—to their use in research may be used for that purpose. In NBAC's judgment, where the research uses identified or coded samples from previously collected specimens, such uses usually are not justified without the source's consent, because the risks to sources and others may be more than minimal. However, the use of unidentified or unlinked samples for research could be justified in some cases if other appropriate protections were in place, despite the lack of informed consent.

A second challenge arises when individuals are asked to provide samples for possible use in future research, even though an approved research protocol does not yet exist. Clearly, individuals cannot give specific, informed consent today to the use of their materials some time in the future, although some form of "prospective authorization" may still be possible. In a separate report, NBAC considered whether persons while competent should be

permitted to give a "prospective authorization" to participation in research if they should lose their capacity to consent (NBAC 1998). NBAC recognized that, within limits and with other appropriate protections, individuals could give prospective authorization to a particular class of research if its risks, potential direct and indirect benefits, and other pertinent conditions have been explained. Allowing individuals to express their preferences for future research is consistent with respecting persons, and it may be less problematic when the research will be conducted not on their bodies but on biological materials they have provided, when the risks are mainly psychosocial, when the risks are minimal or can be minimized—for example, through unidentified or unlinked use—and when the risks have been explained to potential sources who then provide their biological materials for this purpose.

Objectionable, Unacceptable, or Questionable Research

Individuals and groups also may have an interest in the type of research in which a sample is to be used, and some may find the intended use of the knowledge that would be gained by the research to be objectionable. For example, for religious or cultural reasons, some may believe that their biological materials should not be used in contraceptive research or in studies that are aimed at identifying individuals who are prone to violence or other socially unacceptable behaviors. Some individuals may object to the possibility that researchers could sell their samples to companies for profit. Still others may have concerns if the materials were obtained in an unusual or deceptive manner. Or, some individuals or groups, such as some Native Americans, may have strong beliefs about the integrity of the body, whether living or dead.[4]

Postmortem Uses of Biological Materials

Many existing biological materials have been obtained from individuals who are long dead, and the plain truth is that any specimen stored long enough will outlast its source. It might be thought that once the source is dead, no interests remain that require protection, but for a number of reasons, this is not the case. For example, the decedant's family or other loved ones may have an interest in how the material is used, or members of the source's ascriptive group may have an interest in what happens to it. Furthermore, individuals may have interests that survive their deaths, such as the interest in what happens to their children and grandchildren after they themselves die. Similarly, persons may have an interest in the uses to which their biological materials are put, whether these uses occur before or after their deaths. This may be true especially if they consider certain uses impermissible per se, based on their deepest, life-long religious or ethical values. In addition, new information obtained about persons after they have died may affect the memories, perspectives, and relationships of family members and others.

Even if, strictly speaking, the dead do not have interests that require protection, the living may want to establish policies to ensure that some of these outcomes do not occur (DeRenzo, Biesecker, and Meltzer 1997). Such policies could be viewed as means of reducing the worries of the living about what might happen after their deaths. Thus, a policy of unrestricted access to the stored specimens of deceased persons cannot be justified on the grounds that no ethical issues are at stake (Nelkin and Andrews 1998). If people restrict use of their materials when they are still alive, those restrictions also should apply after their deaths. (Chapter 3 provides a discussion of the current regulatory perspective on this issue.)

Just Institutions, Policies, and Practices

Although in the past the principle of justice has been neglected relative to the other Belmont principles—beneficence and respect for persons—in recent years it has come to the forefront. Justice requires the fair and equitable distribution of benefits and burdens in research, in accord with both the formal criterion of treating similar cases in a similar way and various material criteria that specify relevant similarities and differences among individuals and groups (Beauchamp and Childress 1994). More broadly, justice in the context of genetics concerns "the protection of individual persons and cultural groups from unjust social prejudices and arrangements that would burden individual choice or

degrade the worth of certain groups defined in invidious ways" (Murphy and Lappe 1994). In addition, as previously noted, the risks of discrimination in health insurance and employment raise significant questions about whether institutions and policies are just.

Some of the ethical concerns regarding the research use of human biological materials fall under more than one general principle. For example, justice may require that certain procedures are in place that will ensure fair participation on the part of a particular group in designing research protocols that may have a negative impact on that group. Indeed, justice, along with the other two Belmont principles, should be interpreted to include communities as well as individuals. Just as beneficence may require attending to group harms, and respect for persons may necessitate attending to their communities, so justice may mandate the provision of procedures for group participation in the planning of research.

Questions arise about just patterns of distribution of both the burdens and the benefits of research involving human biological materials. Insufficient attention has been paid to justice in the selection of sources of specimens for research purposes. For example, specimens may be collected from a given population because that population is at risk for a certain genetic condition. Once those specimens are collected in a repository, it may be easier to conduct future, unrelated studies on the stored tissue instead of collecting a new set of specimens from a more representative spectrum of society. As a result, the population that originally provided the specimens may bear the burden of additional research, with the risk of being stigmatized for disease susceptibility, largely because its specimens were readily available for research. Justice requires that further attention be paid to ways in which the burdens and risks of research can be distributed more equitably.

The weight that should be accorded society's interest in the benefits of applied biomedical research also will depend in part upon how widely these benefits are distributed and to whom. If the distribution of benefits is grossly inequitable, it is misleading to speak of a common interest in medical progress. Consequently, the case for tolerating increased risks to the interests of those who provide specimens for the sake of society's interest in medical progress becomes weaker if some people—including some who provide the biological materials—lack access to important health care benefits because they cannot afford them. Nevertheless, if significant benefits of medical progress accrue to a large number of people or to those suffering from rare, but debilitating or lethal diseases, a societal interest is relevant, even if not all benefit or not all benefit equally. Furthermore, potential benefits of that research may accrue to future generations, raising issues of intergenerational justice.

Some of the possible policies that could be adopted to protect the sources of biological materials and others from wrongs and harms likely will require increased expenditures for research. However, a just distribution of the burdens of research requires this investment, when needed and within appropriate limits, to reduce those wrongs and harms. A just distribution also can help ensure public trust in research and facilitate public contributions of biological materials to important research endeavors. Elsewhere, NBAC has recommended that if additional protections are required for human subjects in research, all who support the research, from both the public and the private sectors, should work together to ensure that sufficient resources are made available (1998).

Commodification of the Body and Its Parts: Issues of Justice and Respect for Persons

The distribution of the financial gains that may be realized through various uses of human biological materials raises a number of concerns. Some individuals and groups have sought to share in the profits that are generated by patentable biologic inventions that were developed with the use of their biological materials. Perhaps the most famous case is that of John Moore, who claimed a financial interest in the cell line that was developed from his spleen tissue.[5] The California Supreme Court rejected Moore's claim and hence any claim to a portion of the profits derived from uses of the cell line. However, it did affirm that the physicians who used Moore's spleen tissue to develop the cell line had a duty to disclose this fact to him in advance.

The two parts of the ruling mark an important distinction between the following questions: 1) Is the individual entitled to some or all of the profits that are realized from a product in the development of which his or her biological specimen played a role? and 2) Is the individual entitled to disclosure of the fact that his or her biological sample may be used to develop a profitable item, and can that individual refuse to allow such uses? These questions suggest that two distinct interests are present: the financial interest in profiting from the use of one's sample and the interest in knowing whether one's physician or the researcher has an ancillary financial interest that might change or even compromise his or her professional conduct. The second interest, although less tangible than the first, may be extremely important to some individuals, who may want to be aware of and perhaps take steps to avoid health care relationships that are characterized by significant conflicts of interest or to decline to participate in such studies.

Apart from the legal ruling in this case, the generation and distribution of profits from human biological materials may raise for some individuals and groups fundamental conceptions of distributive justice. From some perspectives, it would be misleading to refer only to the interest that individuals have in a share of the profits derived from uses of their biological samples and whether this interest should be recognized as a legal property right. According to some commentators, individuals not only have an interest but also a property right, because their tissues, blood, and DNA are their property.

Some moral philosophers have assumed or argued that a person's body is his or her property, in the sense of a moral property right (Locke 1963). The model of the body as "property" stems from a claim of self-ownership and seeks to authorize individuals to exercise control over the use and disposition of their body and body parts (Andrews 1986). This view tends to treat the body as incidental rather than as intrinsic to personal identity, and it allows the transfer of organs and tissues to others by donation or sale without compromising the nature of the self. However, as the Moore case demonstrates, conflict can arise when, for example, a patient and a researcher assert competing claims or "property rights" to excised body tissues. By contrast, some cultural and religious traditions in the United States hold that the body and its parts are not reducible to property that can be bought and sold, even though they may be donated for research and other purposes (Murray 1987). The conflicting religious and philosophical traditions that inform the discussion of the body as property render this a topic that deserves fuller consideration in another context. For the purposes of this report, however, it is sufficient to note that these conflicting traditions form a background against which the research use of human biological materials can be considered.

Summary

Any ethically sound policy for research uses of human biological materials must reflect a defensible balance of the ethical reasons that support greater control over the use of human biological materials and stronger protections for subjects, on the one hand, and the ethical reasons that support greater access to samples for purposes of conducting clinically beneficial research and/or clinical interventions, on the other hand. These reasons will vary in weight and impact depending on the identifiability of the sample sources and on the probability and magnitude of various wrongs and harms that may occur.

The major ethical reasons that support greater control over the use of human biological materials by sources and the institution of more rigorous safeguards against harms and wrongs that may occur to sources include avoiding discrimination in insurance and employment, stigmatization, group harms, familial conflicts (including those of the survivors of the deceased), and uses that are objectionable to the source. As this chapter indicates, it may be possible to avoid or at least greatly reduce the risk of some of these harms and wrongs by developing, for example, stronger protections of privacy and confidentiality. Rather than assuming that a necessary conflict exists between promoting important research and protecting biological sample sources and others against various wrongs and harms, NBAC holds that policymakers should seek—with the widest possible public and professional participation—to develop policies that avoid tradeoffs, while recognizing and setting procedures to

deal with situations that sometimes necessitate such trade-offs, especially those involving less weighty interests. The recommendations that follow in the next chapter indicate some possible directions for policies that can both promote important research and provide sufficient safeguards for the rights and welfare of sources of biological materials and their families, groups, and communities.

Notes

1 See Buchanan, A., 1998, "An Ethical Framework for Biological Samples Policy" and Campbell, C., 1997, "Research on Human Tissue: Religious Perspectives." These background papers were prepared for NBAC and are available in Volume II of this report.

2 Remarks by President Clinton. The White House, July 14, 1997.

3 Knoppers, B., M. Hirtle, S. Lormeau, C.M. Laberge, and M. Laflamme, 1997, "Control of DNA Samples and Information." This background paper was prepared for NBAC and is available in Volume II of this report.

4 Dukepoo, F., "Sensitivities and Concerns of Research in Native American Communities." Testimony before NBAC. July 14, 1998. Portland OR.

5 *Moore v. Regents of California et al.*, 793 P.2d 479 (Cal. 1990).

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Chapter Five

Conclusions and Recommendations

Introduction

Ethical researchers must pursue their scientific aims without compromising the rights and welfare of human subjects. Achieving such a balance is a particular challenge in rapidly advancing fields, such as human genetics, in which the tantalizing potential for major advances can make research activities seem especially important and compelling. At the same time, the novelty of many of these fields can mean that potential harms to individuals who are the subjects of such research are poorly understood and hence could be over- or underestimated. This is particularly true of nonphysical harms, which can occur in research conducted using previously collected human biological materials when investigators do not interact directly with the persons whose tissues, cells, or DNA they are studying.

Research sponsors, investigators, and Institutional Review Boards (IRBs) thus must exercise great care and sensitivity in applying professional guidelines and government regulations to protect subjects whose biological materials are used in research. Properly interpreted and carefully modified, present federal regulations can protect subjects' rights and interests and at the same time permit well-designed research to proceed using materials already in storage as well as those newly collected by investigators and others. Fundamentally, the interests of subjects and those of researchers are not in conflict. Rather, appropriate protection of subjects provides the reassurance that is needed if individuals are to continue to make their tissue, blood, or DNA available for research. Indeed, public confidence in the ethics and integrity of the research process translates into popular support for research in general.

For many, the central issue in research that involves the use of human tissues and cells is the harm that may occur when private information about the subject's present or future health status—often previously unknown even to the subject—is revealed. One simple protection for subjects would be to render anonymous all human biological materials used in research. That approach would, however, curtail many valuable investigations. Instead, the protection of human subjects should take into account the great value for many studies that use human biological materials of having access to a certain amount of personal and clinical data regarding the persons from whom the specimens were obtained. In other words, the policies and guidelines governing human subjects research should permit investigators—under certain circumstances and with the informed, voluntary consent of sample sources—to have access to identifying information sufficient to enable them to gather necessary data regarding the sources. Provided that adequate protections (which usually, but not always, include informed consent) exist, such information gathering could include ongoing collection of medical record data and even requests for individuals to undergo tests to provide additional research information. In some cases, it even will be acceptable for investigators to convey information about research results to the persons whose samples have been studied. When identifying information exists, however, a well-developed system of protections must be implemented to ensure that risks are minimized and that the interests of sources are protected.

Finally, any system of regulation is most likely to achieve its goals if it is as clear and as simple as possible. This is especially true in the research use of human biological materials, because the federal protections for

research subjects require investigators to outline the involvement of human subjects in their studies and to undergo institutional review of their protocols. Thus, one reason to modify regulations is to clarify which protocols are subject to what sorts of prior review; likewise, illustrations and explanations may be useful in clarifying how the regulations apply to novel or complicated fields that use human biological materials.

How well does the existing Federal Policy for the Protection of Human Subjects (the so-called Common Rule, codified at 45 CFR Part 46) meet these objectives? Specifically, does it provide clear direction to research sponsors, investigators, IRBs, and others regarding the conduct of research using human biological materials in an ethical manner? The National Bioethics Advisory Commission (NBAC) finds that it does not adequately do so. In some cases, present regulatory language provides ambiguous guidance for research using human biological materials. For example, confusion about the intended meanings of terms such as "human subject," "publicly available," and "minimal risk" has stymied investigators and IRB members.[1] Beyond these ambiguities, certain parts of current regulations are inadequate to ensure the ethical use of human biological materials in research and require some modification. This chapter provides interpretations of several important concepts and terms in the Common Rule and recommends ways to strengthen and clarify the regulations and to make their implementation more consistent.

The goals of these recommendations are to address perceived difficulties in the interpretation of federal regulations and in the language of the position statements of some professional organizations; to ensure that research involving human biological materials will continue to benefit from appropriate oversight and IRB review, the additional burdens of which are kept to a minimum; to provide investigators and IRBs with clear guidance regarding the use of human biological materials in research, particularly with regard to informed consent; to provide a coherent public policy for research in this area that will endure for many years and that will be responsive to new developments in science; and to provide the public (including potential research subjects) with increased confidence in research that makes use of human biological materials. To accomplish these goals, NBAC makes 23 recommendations in the following areas:

- adequacy and interpretation of existing federal policies for the protection of human subjects,
- informed consent,
- waiver of consent,
- reporting of research results to subjects,
- consideration of potential harms to others,
- publication and dissemination of study results,
- professional education and responsibilities, and
- federal and state legislation governing medical record privacy.

(See Appendix D for flow charts that illustrate NBAC's recommendations and existing regulations regarding research using human biological materials.)

Research Governed by the Federal Regulations: Activities Beyond Clinical Care

In order to come under the purview of the current federal regulations, an activity must be considered research, as opposed to being considered a clinical intervention. The regulations do not apply to purely clinical uses of human biological materials or to other activities such as quality control procedures or teaching. Rather, they apply to research defined as "a systematic investigation designed to develop or contribute to generalizable knowledge" (45 CFR 46.102(d)). Examination of stored materials undertaken solely as part of a clinical intervention—as when a pathologist assesses a biopsied specimen to confirm a diagnosis—falls outside the purview of the regulations and of this report. But any study conducted on materials that remain from a clinical intervention is subject to the federal research regulations if the investigator is subject to those regulations, if the research is otherwise regulated by the FDA, or if the institution has agreed not to supply samples for research without following the federal regulations.[2] As investigators make greater use of human biological materials in a wide range of research projects, specimen repositories must understand and adhere to federal regulations.

Interpretation of the Existing Federal Policy for the Protection of Human Subjects

In the context of studies that use human biological materials, the lack of clarity regarding several key regulatory terms means that they cannot provide the guidance needed by investigators, IRBs, and others. These terms include "human subject," "existing and publicly available," "identifiable," "minimal risk," "rights and welfare," and "practicable." In addition, it is not always clear which types of research are exempt from IRB review or consent requirements.

Criteria for Exemption from Review

Ordinarily, when an identifiable individual is the subject of research, the regulations require IRB approval of the study. But circumstances do exist in which this protection is unnecessary. The regulations provide two conditions under which research with human biological materials from living individuals may be exempt from IRB review, consent requirements, and other protections. These conditions are when the samples "exist and are publicly available and when the samples exist and information is recorded by the investigator in such a manner that sources cannot be identified either directly or through identifiers linked to the sources" (45 CFR 46.101 (b)(4)). The determination that a study is eligible for exemption is made by the IRB administrator or other institutional official. Of course, there are times when eligible studies should not be granted an exemption, because IRB review would be wise even if not required.

Logically, however, the first determination to be made when considering whether a research protocol is subject to review is whether one or more human subjects (as defined by federal regulations) are involved. If so, review may be required, unless the samples are "existing and publicly available." Each criterion is discussed below.

What Is a Human Subject? The "Identifiability" of Samples and the Applicability of the Common Rule

Although studying human blood or tissue at first does not appear to be the same as studying a human subject, the examination of blood or tissue can yield information about the person from whom it was obtained. Thus, even the study of discarded surgical waste can be a form of human subjects research. The federal regulations define a human subject as "a living individual about whom an investigator conducting research obtains: (a) data through intervention or interaction with the individual, or (b) identifiable private information."[3] Section 46.102(f)(2) defines identifiable to mean that "the identity of the subject is or may readily be ascertained by the investigator or…associated with the information." The Office for Protection from Research Risks (OPRR) interprets "identifiable" to include specimens with codes that, with the cooperation of others, could be broken in order to reveal the identity of the tissue source (1993).

The academic and professional literature on the research use of human biological materials includes a variety of terms to describe the identifiability of research samples. Part of the confusion about the interpretation of the term "identifiable" arises from the fact that people sometimes refer to the state of the information attached to the biological material in the repository (i.e., the *specimen*) and sometimes refer to the material (i.e., the *sample*) and the accompanying information that is provided to the researcher. For example, the specimen might be identified in the repository, but no identifying information is forwarded with the sample sent to the researcher. This distinction is of considerable importance, because the potential for both benefit and harm is greater when the sample is directly or easily linked to the person who provided the specimen, placing the burden of protection in different places depending on who has access to the information (e.g., the researcher, the pathologist, or both). If samples are identifiable, the potential exists for the investigator or a third party (e.g., insurer, employer) to contact the subject or to act in some way that might affect the subject. For example, an investigator might want to contact an individual to gather more medical information, obtain consent for additional or different uses of the sample, provide information about the results of the study, or communicate findings that might be of clinical significance to that individual. Furthermore, because current federal regulations define a human subject as a "living individual," research using stored specimens from people who have died would not come under the regulatory protection for human subjects.[4]

As noted in Chapter 2, NBAC adopted the following definitions regarding the diverse status of human biological materials, depending upon whether they are sitting in storage in a repository or whether some of the material from a repository has been selected for research purposes. These definitions were developed to help clarify the meaning of the term "identifiability" for the purposes of interpreting the federal regulations.

Repository collections of human biological materials (i.e., specimens) consist of two types:

- Unidentified specimens are those for which identifiable personal information has not been collected or, if collected, was not maintained and cannot be retrieved by the repository.
- Identified specimens are those linked to personal information in such a way that the person from whom the material was obtained could be identified by name, patient number, or other information (e.g., his or her relationship to a family member whose identity is known).

Research samples are the collections of human biological materials provided to investigators by repositories or collected by investigators in the process of conducting research. Such materials can be categorized into at least four types, which are differentiated by the amount of information that is conveyed to the investigator about the person from whom the sample was obtained. NBAC defines the different types as follows:

- Unidentified samples—sometimes termed "anonymous"—are those supplied by repositories to investigators from a collection of unidentified human biological specimens.
- Unlinked samples—sometimes termed "anonymized"— are those that lack identifiers or codes that can link samples to identified specimens or particular individuals. Typically, repositories send unlinked samples from identified human biological specimens to investigators without identifiers or codes so that identifying particular individuals through the clinical or demographic information that is supplied with the sample or biological information derived from the research would be extremely difficult for the investigator, the repository, or a third party. Unlinked samples also include those that are already in an investigator's possession and whose identifiers have been removed by a disinterested party.
- Coded samples—sometimes termed "linked" or "identifiable"—are those supplied from identified specimens by repositories to investigators. However, these samples do not include any identifying information, such as patients' names or Social Security numbers. Rather, they are accompanied by codes. In such cases, although the repository (or its agent) retains the ability to link the research findings derived from a sample with the individual source by using the code, the investigator (or one reading a description of the research findings) would not be able to do so.
- Identified samples are those supplied by repositories from identified specimens with personal identifiers (such as names or patient numbers) that are sufficient to allow the researcher to link directly the biological information derived from the research with the individual from whom the material was obtained.

The second criterion for exemption from the Common Rule (that the samples are existing and that the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or indirectly through identifiers) reflects an underlying premise of the federal regulations, namely that protection is needed when research results can be linked to specific human subjects. Thus, it would be appropriate for research on unlinked samples to be exempt from IRB review under most circumstances.

"Existing and Publicly Available" Materials

Regarding the first exemption (that the materials are existing and publicly available), OPRR interprets the term "existing" to mean any materials that already have been collected—that is, materials that are "on the shelf"—at the time the research is initiated, whether collected for previous research or nonresearch purposes (OPRR 1993). Existing samples are thus differentiated from samples to be collected at a later date as a part of the research protocol in question.

The second criterion in the first exemption—the requirement that samples be "publicly available"—is more problematic. The reasons for exempting publicly available data from the purview of the Common Rule are

that individuals have no expectation of privacy regarding information to which anyone can gain access and that any harm that may be associated with the disclosure of such information already has occurred and should be the responsibility of those who collected the data and made them public. Well-known examples of sources of publicly available information include telephone books and land title records; however, it is not clear what kinds of biological materials might be considered publicly available.

In response to a request for clarification, OPRR defined publicly available to mean that "unrestricted access on demand (i.e., unrestricted availability subject only to limited quantities and/or related costs) may be considered a reasonable basis for claiming that a material is 'publicly available.'"[5] Yet, this interpretation provides minimal guidance, because it is not clear which public is the relevant one (e.g., the general public, the scientific community) and whether available means the same thing as accessible.

Large repositories, often cited as examples of public collections, have in place "strict policies to ensure that cultures are distributed only to qualified organizations and researchers with legitimate and justifiable scientific uses for these materials."[6] Thus, the biological materials are available not to anyone, but in general are restricted to those who have legitimate research interests in their use and presumably possess the capability to perform sophisticated scientific studies that can reveal biological information about the samples or even health-related information about the persons from whom they came.[7]

Although collections might be widely and appropriately available to the research community, it appears that they are rarely available to any member of the public. Thus, the fact that researchers can readily access the specimens does not make them publicly available as that term is commonly understood. Despite the fact that the materials exist in collections and are accessible to researchers, the sources may well have an expectation of privacy, including an expectation that the use of their specimens is subject to regulation and, at times, dependent upon their consent.

It should be noted that the current regulatory policy made sense in the context for which it was first created—for example, a social or behavioral scientist who is using information about people that can be found in directories or newspapers or observed in recordings made of their conduct in public settings. However, the exemption would contradict the purpose of human subjects protection were it applied to innovative biological analyses of stored human tissues or cells. This is because the information that may emerge from such a process is not existing in any genuine sense, much less publicly available.

Thus, NBAC concludes that publicly available materials are those that are available to members of the general public, not merely to specialists, researchers, or other "qualified" persons. Although the accessibility of specimens is an important consideration in specifying appropriate levels of protection, more important considerations include 1) whether the specimens are stored with codes, links, or identifiers, 2) whether identifiable samples (coded or identified) are delivered to investigators for study, and 3) whether the repositories or retainers of the specimens require any assurance that the research will be conducted in a manner that will protect the rights and interests of the sources.[8]

NBAC offers the following recommendations to improve the interpretation and implementation of the existing federal regulations as they apply to research using human biological materials.

Recommendation 1:

Federal regulations governing human subjects research (45 CFR 46) that apply to research involving human biological materials should be interpreted by OPRR, other federal agencies that are signatories to the Common Rule, IRBs, investigators, and others, in the following specific ways:

a) Research conducted with unidentified samples is not human subjects research and is not regulated by the Common Rule.

b) Research conducted with unlinked samples is research on human subjects and is regulated by the Common Rule, but is eligible for exemption from IRB review pursuant to 45 CFR 46.101(b)(4).

c) Research conducted with coded or identified samples is research on human subjects and is regulated by the Common Rule. It is not eligible for exemption unless the specimens or the

samples are publicly available as defined by 45 CFR 46.101(b)(4). Few collections of human biological materials are publicly available, although many are available to qualified researchers at reasonable cost. Therefore, OPRR should make clear in its guidance that in most cases this exemption does not apply to research using human biological materials.

OPRR should issue appropriate guidance for investigators and IRBs regarding these definitions and interpretations or should, if necessary, modify the language of the Common Rule.

NBAC recognizes that costs may be associated with these interpretations of what constitutes a human subject and believes that costs incurred by the investigator to satisfy this requirement should be considered valid and reimbursable expenses by the funding agency. However, NBAC does not believe that these interpretations of the criteria for exemption and review will impede research. Rather, they will ensure that research conducted on coded or identified samples, even if widely available, will be subject to the federal policy of protections.

Expedited Review

The current federal regulations appear to make eligible for expedited review research on materials that will be collected for clinical purposes or those that will be collected in noninvasive or minimally invasive ways for research purposes. Ambiguity in the language, however, appears to make research on existing collections eligible for expedited review only when they were developed for nonresearch purposes. NBAC finds that there is no need to distinguish between collections originally created for clinical purposes and those created for research purposes. In both cases, research on the collected materials should be eligible for expedited review if the research presents no more than a minimal risk to the study subjects. (See the discussion of minimal risk below.)

Recommendation 2:
OPRR should revise its guidance to make clear that all minimal-risk research involving human biological materials—regardless of how they were collected—should be eligible for expedited IRB review.

Special Concerns About the Use of Unlinked Samples

Several repositories maintain a record of the persons from whom specimens were derived so that the repository can track which samples are sent to a clinician or researcher. Such samples may be numbered in such a way that even the repository cannot link the sample to its source. Or, samples might be numbered in such a way that although the repository could confirm that a sample was sent, if the investigator were to ask the repository for additional material or clinical information specific to that source, the repository would not be able to match the request with a specific specimen. The repository could send the investigator a duplicate set of the initial "batch" of samples, but again with no linking data. However, in some rare cases the study sample size might be so small and the findings so unique that it would be relatively easy to identify individuals even if their samples were not linked. Investigators and repositories should scrutinize these situations carefully in order to reduce the risk that sources could be identified. In such instances, it may be more appropriate to use only unidentified (not merely unlinked) samples, to increase the sample size, or even to consider the samples to be identifiable rather than unidentifiable.

When researchers use unidentified and unlinked samples, it is extremely difficult if not impossible for them to contact the source. According to the federal regulations, research using existing samples of this type is eligible for exemption from IRB review. The justification for these regulations appears to be that because it is not possible to contact the sources to ask their permission or gain their consent to any specific uses of their tissues, and because the potential for harm effectively disappears because of a lack of specific identifiability, no special restrictions on the use of such samples should apply.

Although at first glance this seems reasonable, some controversy continues in the case of samples that have been unlinked before being sent to the investigator. Some might consider it ethically problematic that by having the identifiers stripped, the investigator loses the opportunity to obtain consent, as further contact would be impossible. In addition, it is incorrect to assume that because the sources cannot be identified they cannot be harmed or wronged. Some interests of the sample sources may be

harmed even if they are not completely identifiable, and interests of others also may be at risk. For example, there may be group or family interests that could be revealed or placed at risk because of research that is conducted on a class of similar, albeit individually unidentifiable, samples. Individuals have an interest in avoiding uses of their tissues that they regard as morally impermissible or objectionable. Thus, were their materials to be used in research that they would consider objectionable, it is possible that some individuals could be wronged, if not harmed. NBAC recognizes that these concerns are valid, but does not find that they are sufficiently substantial to restrict further use of such samples.

Because the samples are not linkable to individuals, some of the most important arguments that weigh in favor of restricted access do not apply. If the individual cannot be identified, there is little or no risk of insurance or employment discrimination, stigma, adverse psychological reactions, or familial conflict. Thus, to that extent, the case for not allowing use of unidentified and unlinked stored samples is significantly weakened. However, the possibility remains that research findings might still result in potential harms to groups or classes of individuals (e.g., loss of health insurance coverage for individuals found to share a particular trait or characteristic). Although the current regulations do not require investigators to consider such risks to groups, good practice might, in some cases, warrant an effort to minimize risks to others through consultation with relevant groups, alterations in research design, or greater care in the manner in which research results are reported. (See also Recommendations 11, 17, and 18.)

Previous guidelines and reports (see Chapter 3) have categorized samples by the conditions under which they are stored (with or without identifiers). Current federal regulations permit researchers to take existing samples, render them anonymous by removing identifiers, and then use them in research without seeking consent. It is apparent to NBAC that some investigators incorrectly interpret the regulations to mean that so long as they do not know the identity of the sample source, even if the sample is coded (linked), the research is exempt from IRB review.

Given the importance of society's interest in treating disease and developing new therapies, a policy that unduly restricts research access to these unidentified and unlinked samples would severely hamper research and could waste a valuable research resource. As noted in Recommendation 1, research using unlinked samples may be exempt from review; however, if coded or identified samples are rendered unlinked by the investigator, special precautions are in order.

Recommendation 3:
When an investigator proposes to create unlinked samples from coded or identified materials already under his or her control, an IRB (or other designated officials at the investigator's institution) may exempt the research from IRB review if it determines that

a) the process used to unlink the samples will be effective, and

b) the unlinking of the samples will not unnecessarily reduce the value of the research.

The IRB or reviewing body should exercise particular care when the process of unlinking is not carried out by a third party (such as the independent repository that supplied the samples) but rather by the investigator or someone working with or for the investigator. What matters is the outcome—that results from analysis of the samples cannot be linked to their sources—rather than the unlinking method used. Institutions and organizations that participate in research conducted with unlinked samples should establish policies and procedures (e.g., the use of independent third parties to unlink samples) to ensure that the unlinking occurs.

Although unlinking reduces the risk of injury to the specimen sources, it cannot eliminate such risk, which is an especially serious consideration if the unlinking reduces the scientific value of the research (thereby lowering the benefit-to-risk ratio). Generally, it is NBAC's view that when it is feasible to conduct human biological materials research that is in accordance with the usual protections for research subjects, it is preferable to do so, rather than to unlink the samples in order to circumvent those protections.

Exemption from review should not be granted when IRB review would help investigators avoid inflicting harms upon groups (see Recommendation 17) or when the scientific merit of the research is compromised by the

failure to use coded or identified samples with appropriate human subjects protections.

Requirements for Investigators Using Coded or Identified Samples

Within the "identifiable" category of samples are two subcategories: coded samples and identified samples (i.e., where the sample source is expressly identified to the investigator). Within the first category, a distinction may exist between the information provided to the investigator and that held by the repository. For example, the samples might be encoded in such a way that the investigator cannot identify the sample source, but the entity storing the specimen from which the sample has been derived—such as a pathologist or DNA bank—can link the specimen source to the sample that was sent to the investigator. Thus, the code could be broken. Although identifying the source may be more difficult in the latter scenario, because the possibility of linkage remains and elevates the potential for harm, NBAC considers these samples to be identifiable. It is important to note, however, that the ease of identifying the source is part of the calculus in determining the overall level of risk posed by the research.

Repositories and IRBs share responsibility with investigators to ensure that research is designed and conducted in a manner that appropriately protects human subjects from unwarranted harms.

Recommendation 4:
Before releasing coded and/or identified samples from its collection, a repository should require that the investigator requesting the samples either provide documentation from the investigator's IRB that the research will be conducted in compliance with applicable federal regulations or explain in writing why the research is not subject to those regulations.

Recommendation 5:
When reviewing and approving a protocol for research on human biological materials, IRBs should require the investigator to set forth

a) a thorough justification of the research design, including a description of procedures used to minimize risk to subjects,
b) a full description of the process by which samples will be obtained,
c) any plans to obtain access to the medical records of the subjects, and
d) a full description of the mechanisms that will be used to maximize the protection against inadvertent release of confidential information.

When an investigator obtains access to a patient's medical records, either to identify sample sources or to collect additional medical information, human subjects research is being conducted. IRBs should adopt policies to govern such research, consistent with existing OPRR guidance related to medical records research.

Using Previously Obtained Informed Consent and Reconsent

Research using coded or identified samples requires the consent of the source, unless the criteria for a consent waiver have been satisfied. Unfortunately, the consent signed at the time the specimen was obtained may not always be adequate to satisfy this requirement. Specimens that exist in storage at the time the research is proposed may have been collected under a variety of conditions (e.g., in a clinical setting or as part of an experimental protocol). In some instances, individuals make informed choices about how their sample should be used subsequent to its original research or clinical use. In other cases, for a variety of reasons, individuals may not understand fully or may not have been given the opportunity to consider carefully how their specimens may be used in the future. When research is contemplated using existing materials, the expressed wishes of the individuals who provided the materials must be respected. Where consent documents exist, they may indicate whether individuals wanted their samples to be used in future research, and in some instances they may specify the type of research.

IRBs should use the following criteria to evaluate the applicability of such documents to the proposed research:

- Does the language or context of the consent form indicate that the source was interested in aiding the type of research being proposed?

- If the source consented to the sample being used in unspecified future studies, is that consent adequate for the type of research being planned, given the circumstances under which the sample was collected (e.g., whether the sample was requested by a treating physician or whether the consent form offered alternatives to allowing the sample to be used in future studies)?

In some cases, an IRB may determine that an existing consent form permitting unspecified future uses is sufficient. For example, Clayton et al. argue that, "[e]ven in the absence of specific language about DNA testing, it may be appropriate to infer consent if the source wished for the sample to be used to determine why his or her family had a particular inherited disorder" (1995). In such cases, investigators should consider informing subjects that research is occurring and in certain cases also give subjects the opportunity to "opt out." Rarely, however, does the language that is included in typical surgical and other hospital consent forms provide an adequate basis for inferring consent to future research.

Although an opt-out policy provides significant protection for sources and recognizes that their biological material may have been collected without adequate disclosure, it also provides sources with the opportunity to participate in research. When the IRB determines existing consent documents to be inadequate and when the existing sample is identifiable, the individual should be contacted, offered the option of consenting to the specific proposed protocol, and further offered the option of deciding how the sample may be used in the future.

As in the case with research in which new samples are obtained, individuals should be provided with relevant information that will help them decide whether they would like to participate in research. Federal human subjects regulations list the basic elements of informed consent that, of course, also apply when consent is requested for the use of existing samples (45 CFR 46.116(a)). The following points are especially relevant:

- the risks and benefits of participation in the proposed study along with a discussion of the possible consequences of consenting to future identifiable uses of their sample,
- the extent, if any, to which confidentiality will be maintained,
- under what circumstances, if any, sources will be recontacted, and
- an indication that if sources choose to have their samples rendered unidentifiable, they cannot be provided specific information about findings related to their samples.

The rationale for including the option of authorizing future research use of existing samples (rather than mere disclosure that the sample may be used for a wide range of purposes) is that in most cases, existing specimens will have been collected without disclosure. Allowing persons (whose previously collected materials are coded or identified) to choose either to authorize future research use or to have their samples rendered unidentifiable for future use can be viewed as an effort to repair this deficiency. Even if such authorization bears only a remote resemblance to genuine informed consent, it can serve as an expression of respect for persons in the context of proposed uses for existing samples. It is not adequate simply to disclose to persons now that the material already taken from them may be used in the future for purposes of which they were unaware at the time of collection.[9]

Appropriate criteria should be used to determine whether recontacting an individual source is appropriate, and additional concerns should be addressed when developing a plan to recontact any individuals. For example, if explicit consent to use a sample was never obtained (because it met the requirements for waiver), IRBs should consider potential harms that might arise should a subject learn, after the fact, that his or her material had been used in an experiment.

Obtaining New Consent

When human biological materials are collected, whether in a research or clinical setting, it is appropriate to ask subjects for their consent to future use of their samples, even when such uses are at the time unknown. The elements of the consent process for new samples should be the same as those discussed earlier for the use of existing identifiable samples.

Both in the literature and in testimony given before NBAC, discussion has occurred regarding the concerns that arise when administering a consent process in a clinical setting.[10] These concerns often involve the fact that

the stress level may be high in clinical settings, rendering them not conducive to a consent process that involves making complex choices regarding issues that are not related directly to clinical care and that involve speculation about the distant future. In this setting, individuals may be anxious about the clinical procedure they are about to undergo and may not be prepared to consider carefully the factors that go into making informed decisions about the hypothetical research use of their tissues. The fact that individuals also will be faced with making a number of other decisions and with completing paperwork related to the clinical procedures compounds the problem of administering an informed consent process in this setting. A better approach might be to discuss the future research use of an individual's specimen at some point before or after consent is obtained for the clinical procedure.

NBAC acknowledges the important contribution to this discussion of groups such as the National Action Plan for Breast Cancer that have done thoughtful work and made helpful suggestions on ways in which to improve the overall consent process, including its design and timing. However, it is clear that additional studies are needed to determine the best time to administer this consent in clinical settings. As investigators and IRBs consider this issue, it may be useful to consult the work of these groups. Using their guidance and collective experience, the scientific community should develop a consensus regarding a standard method for human biological materials collection in both therapeutic and research contexts—one that would minimize the need for complex efforts to recontact the source.

Whether obtaining consent to the research use of human biological materials in a research or clinical setting, and whether the consent is new or renewed, efforts should be made to be as explicit as possible regarding the uses to which the material might be put and regarding whether it is possible that the research might be conducted in such a way that the individual could be identified. Obviously, different conditions will exist for different research protocols, in different settings, and among individuals. NBAC notes that the current debate about the appropriate use of millions of stored specimens has endured because of the uncertain nature of past consents. NBAC also recognizes that investigators and others who have collected and stored human biological materials now have the opportunity to correct past inadequacies by obtaining more specific and clearly understood informed consent. By doing so, the need to render samples unidentifiable through unlinking may become less frequent, and the need to obtain reconsent thus may be minimized. It is with these considerations in mind that NBAC makes the following recommendations about improving the consent process for the use of human biological materials in research.

Recommendation 6:
When informed consent to the research use of human biological materials is required, it should be obtained separately from informed consent to clinical procedures.

Recommendation 7:
The person who obtains informed consent in clinical settings should make clear to potential subjects that their refusal to consent to the research use of biological materials will in no way affect the quality of their clinical care.

Recommendation 8:
When an investigator is conducting research on coded or identified samples obtained prior to the implementation of NBAC's recommendations, general releases for research given in conjunction with a clinical or surgical procedure must not be presumed to cover all types of research over an indefinite period of time. Investigators and IRBs should review existing consent documents to determine whether the subjects anticipated and agreed to participate in the type of research proposed. If the existing documents are inadequate and consent cannot be waived, the investigator must obtain informed consent from the subjects for the current research or in appropriate circumstances have the identifiers stripped so that samples are unlinked.

Recommendation 9:
To facilitate collection, storage, and appropriate use of human biological materials in the future, consent forms should be developed to provide potential subjects with a sufficient number of options to help them understand clearly the nature of the decision they are about to make. Such options might include, for example:

a) refusing use of their biological materials in research,

b) permitting only unidentified or unlinked use of their biological materials in research,

c) permitting coded or identified use of their biological materials for one particular study only, with no further contact permitted to ask for permission to do further studies,

d) permitting coded or identified use of their biological materials for one particular study only, with further contact permitted to ask for permission to do further studies,

e) permitting coded or identified use of their biological materials for any study relating to the condition for which the sample was originally collected, with further contact allowed to seek permission for other types of studies, or

f) permitting coded use of their biological materials for any kind of future study.*

Obtaining consent to future research on stored biological materials is difficult because it is impossible to foresee many studies that may be designed in the future. Also, patients may agree to have their biological materials used in some types of studies, but not in others. Consent to future research is meaningful only if patients appreciate, as much as possible, the types of studies that may be conducted. However, describing future research in detail may be confusing rather than helpful, especially in the clinical setting, and could be administratively

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* Commissioner Capron does not believe that (e) or (f) should be included among the options offered to potential subjects. IRBs are supposed to ensure a favorable risk-benefit ratio in all approved research, and subjects are supposed to be given accurate and understandable information prior to providing consent to participate in a study. Because options (e) and (f) encompass future studies with unknown risks and benefit, neither adequate IRB review nor informed consent is possible at the time when subjects are asked to provide consent for the future use of stored material. Commissioner Shapiro concurs with this view regarding option (f) only. In the case of option (e), the range of studies is limited to "any study relating to the condition for which the sample was originally collected," but even this definition will not remedy the problem, in Commissioner Capron's view. As for option (f), the use is confined to "coded" samples rather than the "identified" samples permitted in option (e), but one premise of this report is that "coded" samples should be grouped with identified samples because information produced from analyzing them potentially can be linked to identifiable persons.

Commissioner Miike offers the following statement: "Recommendation 9 identifies the range of prospective consents that the Commission has determined are reasonable for patients and research participants to assess and either assent to or decline. While the report does not necessarily make this explicit, at least my interpretation is that these are not being offered as a package: i.e., future consent forms need not necessarily include all of these choices, but research institutions and patient care facilities should view these as a kind of menu from which they might revise their current consent forms. In this range of prospective consents, the most controversial is Recommendation 9(f): 'To permit coded use of their biological materials for any kind of future study.' This general consent recommendation would seem to contradict the Commission's overall report, with its focus on consent as truly being informed. [This] report, however, addresses human biological materials collected both in research and clinical care settings. In the research setting, an extensive prospective consent form that includes the entire range identified in Recommendation 9 seems reasonable. Given the nature of current consent documents in the clinical care setting, however, I believe it is unreasonable to expect patients to deal with such a complicated consent form for permissible future research. In the clinical setting, I am primarily concerned with separating the consent to treatment from the consent for possible future use of any biopsied or surgically removed tissues. Patients, whose primary concern is treatment or diagnosis, cannot be expected to reasonably evaluate the diverse range of prospective consent choices as identified in Recommendation 9. Thus, for practical purposes, a general consent form must be used. For those concerned over the use of such a general prospective consent, my response is as follows: For participants in research projects who are asked to consent or decline to give permission for use of their tissues in future research projects, the range of consents identified in Recommendation 9 can be provided. However, for patients in clinical settings, the primary problem currently is that the consent for possible future use in research of any tissue collected is buried in the clinical care consent form. This separate consent should be made explicit by requesting two signatures—one for the clinical care, the other for possible future research uses (see Recommendation 6). As for the specific language of the prospective research use, a complicated document will raise unnecessary concerns and would, I predict, lead to a significant decrease in the availability of such materials. Moreover, this report makes other recommendations which strengthen the current informed consent process. Any general consent would be reviewed when future research projects are undertaken: 1) to assess whether the consent is appropriate in view of the particular research project to be undertaken; 2) the practicability of contacting the tissue donor for updating that consent; and 3) designing the project to strengthen confidentiality and/or to ensure anonymity. Without a general consent option, I am concerned that consent forms in the clinical setting will become too complicated and patients will be overly concerned and opt not to sign. Even when the research will be minimal risk and not require informed consent, such biological materials will be forever lost to research, because they would have been excluded at the time of biopsy or excision from any future research use."

burdensome. The National Institutes of Health (NIH) and advocacy groups such as the National Action Plan for Breast Cancer have worked on designing multilayered consent forms that are both informative and practical. Such efforts should be encouraged and continued.

This policy for existing samples should be supplemented with special attention to areas of research that are considered sensitive or potentially objectionable to some. In other words, even if the source of an identifiable existing sample chooses to render the sample identifiable and authorizes future identifiable research uses, he or she should enjoy the additional protection afforded by the requirement of specific consent to uses of the sample that he or she might consider sensitive or objectionable. Such a category may include, for example, certain behavioral genetics protocols, studies differentiating traits among ethnic or racial groups, or research on stigmatizing characteristics such as addictive behavior.

Criteria for Waiver of Consent

When an investigator proposes to conduct research with coded or identified samples, it is considered research with human subjects. Ordinarily the potential research subject is asked whether he or she agrees to participate. Seeking this consent demonstrates respect for the person's right to choose whether to cooperate with the scientific enterprise, and it permits individuals to protect themselves against unwanted or risky invasions of privacy. But informed consent is merely one aspect of human subjects protection. It is an adjunct to—rather than a substitute for—IRB review to determine if the risks of a study are minimized and acceptable in relation to its benefits.

When a study is of minimal risk, consent is no longer needed by a subject as a form of self-protection against research harms. It is still appropriate to seek consent, however, in order to show respect for the subject, unless it is impracticable to locate him or her in order to obtain it. Thus, when important research poses little or no risk to subjects whose consent would be difficult or impossible to obtain, it is appropriate to waive the consent requirement.

As stated in the current federal regulations, human subjects research is presumed to require consent, but this requirement can be altered or waived if all four of the following criteria, set forth at 45 CFR 46.116(d), are met:

- The research involves no more than minimal risk to the subjects,
- The waiver or alteration of consent will not adversely affect the rights and welfare of the subjects,
- The research could not practicably be carried out without the waiver or alteration, and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Determining the risks of research and the effects that waived consent might have on the rights and welfare of the subject are bedrock considerations in deciding whether a subject's consent is an essential part of human subjects protections. Four key terms are central to this determination: "minimal risk," "rights and welfare," "practicability," and "after participation."

Minimal Risk

The regulations state that "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 exams or tests" (45 CFR 46.102(i)). Identifying minimal research risks thus depends upon a comparison of research risks with risks that persons "ordinarily" face outside of the research context.

However, when considering the risks of research conducted on human biological materials, one may question the applicability of the threshold that the regulations establish for assessing minimal risk. The risks encountered "during the performance of routine physical or psychological exams or tests" have limited utility as a baseline. Although these risks can be compared to the physical risks faced in the collection of new samples, they are not really comparable with the risks of social and psychological harm relevant to research on biological samples. The risks encountered during the performance of a medical exam evidently relate to harms that the intervention itself may produce. The risks of psychosocial harm associated with research on biological samples, on the other hand, relate to future uses of information derived from samples.

The risks of daily life seem a more promising threshold for assessing the risks of research on biological materials.

In research on biological samples, the potential harms of central concern (e.g., stigmatization, insurance and employment discrimination, familial conflict, anxiety, violations of privacy) are those that may result if certain information from biological samples (e.g., the subject's susceptibility to disease) is disclosed to noninvestigators. But such information also commonly is contained in medical records. Persons (research subjects and nonresearch subjects alike) generally face the risk that diagnostic, predictive, and other forms of information about them contained in their medical records will be obtained and used in a harmful manner. Although insufficient data are available to make a decisive statement about the relative probabilities of harm resulting from uses of biological samples vis-a-vis access to medical records, one might hold that the level of risk is similar in both cases. Indeed, research on biological samples arguably poses fewer risks, because the sources of even coded and identified samples may be more difficult to trace than the subjects of explicitly labeled medical records. Thus, one might conclude that the risk involved in the use of biological samples is minimal.

NBAC does not find this analysis of minimal risk to be persuasive. Fundamentally, the issue is not whether the risk of harm that research poses to subjects is in itself minor or substantial; rather, the issue is whether the risks that the research presents are more severe than risks that individuals ordinarily confront. According to this interpretation, research risks could be substantial but nevertheless be considered "minimal." The problem is that the purpose of assessing whether risk is minimal is to help IRBs determine what types of protections should be required. Although a strict reading of the regulations may permit an interpretation that allows one to consider great risks of harm to subjects minimal, such an interpretation certainly violates the spirit of the regulations.

An alternative interpretation of the regulations avoids this result. According to this interpretation, the concept of "'risks of everyday life,' has normative as well as descriptive force, reflecting a level of risk that is not simply accepted but is deemed socially acceptable" (Freedman, Fuks, and Weijer 1993). In addition, any risk that is not socially acceptable cannot properly be characterized as a risk of daily life. There is a widespread view that the present risks of harm from uses of sensitive medical information about individuals are not acceptable and that stronger privacy laws are needed to remedy this situation. Thus, the risks of harm resulting from the improper use of medical records are not, according to this interpretation, risks of daily life. It follows that one cannot employ the risks of harmful uses of medical records as a baseline for determining whether research on biological samples is of minimal risk. This, in turn, makes it difficult to perform a minimal risk analysis for research on biological samples, as there are no apparent alternatives that can plausibly serve as a baseline.

Nonetheless, NBAC believes that most research using human biological materials is likely to be considered of minimal risk because much of it focuses on research that is not clinically relevant to the sample source, as compared to research with medical records, for example, which is likely to be filled with clinically relevant findings that could harm the individual if misused or used inappropriately by third parties.

Although the regulatory definition of minimal risk appears inadequate for research on human biological materials, NBAC recommends that in the assessment of risk, IRBs should consider the following questions when determining the extent to which a source could be harmed:

- How easily identifiable is the source?
- What is the likelihood that the source will be traced?
- If the source is traced, what is the likelihood that persons other than the investigators will obtain information about the source? (Privacy/confidentiality laws may be relevant here, as are the integrity of investigators and their institutional confidentiality protections.)
- If noninvestigators obtain information regarding the source, what is the likelihood that harms will result, including adverse consequences arising from the reporting of uncertain or ambiguous clinical results? (State and federal discrimination laws may be relevant with respect to uses of information by third parties.)

As noted in Chapter 4, the likelihood of psychosocial harms resulting from research on biological samples is somewhat speculative at present. There are, however, reasons to think that the risks of harm are generally

minimal or can be easily rendered minimal. Given current scientific practices, many studies are being conducted in which it is not necessary that investigators know the identity of sample sources. In these cases, investigators will not have a need to trace sample sources although they might require additional clinical information without identifying the source. Even in instances when investigators need to identify a source, it is not necessary to reveal information about sources to third parties. Although it is possible that noninvestigators will access information about a source, investigators can minimize this risk through appropriate confidentiality mechanisms. For example, protocols that include provisions for isolating the results of genetic or other research results completely from the source's medical record and that incorporate a prohibition on returning uncertain or ambiguous information to sources (which would forestall the communication of premature and potentially upsetting information) should in most cases ensure that risks will be minimal.

Recommendation 10:
IRBs should operate on the presumption that research on coded samples is of minimal risk to the human subject if

a) the study adequately protects the confidentiality of personally identifiable information obtained in the course of research,
b) the study does not involve the inappropriate release of information to third parties, and
c) the study design incorporates an appropriate plan for whether and how to reveal findings to the sources or their physicians should the findings merit such disclosure.

Rights and Welfare

Failure to obtain consent may adversely affect the rights and welfare of subjects in two basic ways. First, the subject may be improperly denied the opportunity to choose whether to assume the risks that the research presents, and second, the subject may be harmed or wronged as a result of his or her involvement in research to which he or she has not consented.

A waiver of consent in the collection of new biological samples violates subjects' rights because it would expose them to unwanted bodily invasions. The interest in being free from unwanted bodily invasions is the primary interest the requirement of informed consent was instituted to protect. In the case of consent for the use of existing samples, the interests at stake are different. In this context, it is principally the social and psychological harms delineated in Chapter 4 that are at issue. Subjects' interest in controlling information about themselves is tied to their interest in, for example, not being stigmatized and not being discriminated against in employment and insurance.

Although the risks of psychosocial harms generally may be minor in research on human biological materials, some important and exceptional cases are worth noting. For example, controversial studies such as those that involve behavioral genetics or that make explicit comparisons between ethnic or racial groups are likely to offend some research subjects and may threaten their ascriptive identities. Moreover, there remains the possibility that the results of such studies will be used to stigmatize and discriminate against group members (subjects and nonsubjects alike).

Further, when state or federal law, or customary practice, gives subjects a right to refuse to have their biological materials used in research, then a consent waiver would affect their rights adversely. Medical records privacy statutes currently in place or under consideration generally allow for unconsented research use and could be interpreted to suggest a similar standard for research using human biological materials. But as new statutes are enacted, it is possible that subjects will be given explicit rights to limit access to their biological materials.

Recommendation 11:
In determining whether a waiver of consent would adversely affect subjects' rights and welfare, IRBs should be certain to consider

a) whether the waiver would violate any state or federal statute or customary practice regarding entitlement to privacy or confidentiality,
b) whether the study will examine traits commonly considered to have political, cultural, or economic significance to the study subjects, and
c) whether the study's results might adversely affect the welfare of the subject's community.

Practicability

Even when research poses no more than minimal risk and when a consent waiver would not affect the rights and welfare of subjects, respect for subjects requires that their consent be sought. However, on some occasions, demonstrating this respect through consent requirements could completely halt important research. An investigator who requests a waiver of the informed consent requirement for research use of human biological materials under the current federal regulations must provide to the IRB evidence that it is not practicable to obtain consent. Unfortunately, neither the regulations nor OPRR offers any guidance regarding what defines practicability.[11]

According to the *Oxford English Reference Dictionary*, the term "practicable" is defined, in the ordinary sense, as that which "can be done or used" or is "possible in practice." The issue for regulatory purposes and (NBAC would suggest) for the purpose of assessing the ethical acceptability of this provision, is whether the practicability requirement—alone or in combination with other criteria for obtaining a waiver—adds guidance to the investigators and IRBs that will make these decisions. Informed consent may not be "possible in practice" when there are many more subjects than there are individuals to seek their consent or when the amount of time it would take to recontact a subject or subjects would be longer than the time it would take to complete the study. Similarly, obtaining consent might be considered impracticable if the financial or labor costs of either a direct or indirect recontact effort (such as mailing consent forms and information) far exceeded the researcher's budget. For many research protocols, it is likely to be exceedingly difficult to locate people in order to obtain consent. One might even suggest that in research that is designed to provide a direct benefit to some of the subjects, it would be impracticable to take the time to recontact potential subjects, because the delay in completing the study could be considered a more serious harm than would be the failure to obtain express consent. Although these are reasonable examples of impracticability and, NBAC would suspect, might be regarded by some as good reasons for granting a waiver, the trouble with the practicability requirement is that it forces a comparison between otherwise incommensurable harms: the wrong that could be committed by not obtaining informed consent and the prohibitively costly and perhaps even needlessly intrusive harm of attempting recontact. As with many types of incommensurability in IRB review, the task of assessing risk and benefit becomes far more problematic.

Recommendation 12:
If research using existing coded or identified human biological materials is determined to present minimal risk, IRBs may presume that it would be impracticable to meet the consent requirement (45 CFR 46.116(d)(3)). This interpretation of the regulations applies only to the use of human biological materials collected before the adoption of the recommendations contained in this report (specifically Recommendations 6 through 9 regarding informed consent). Materials collected after that point must be obtained according to the recommended informed consent process and, therefore, IRBs should apply their usual standards for the practicability requirement.

Even in instances when it might be considered practicable to obtain consent for research use of stored human biological materials, it may be burdensome for investigators to do so. NBAC believes that in assessing the appropriateness of waiving consent, consideration should be given principally to the criteria of minimal risks and rights and welfare and that practicability should not be a compelling consideration. Thus, IRBs should be permitted to presume that contacting individuals who were the sources of tissues in the past will be impracticable enough to satisfy the regulatory requirements. Of course, IRBs are free to forego the presumption and require consent to minimal risk research whenever they believe that a demonstration of respect for the subjects is important and that the process will not pose significant burdens on investigators.

NBAC recognizes that if its recommendation that coded samples be treated as though they are identifiable is adopted, there may be an increase in the number of research protocols that will require IRB review. If, however, such protocols are then determined by an IRB to present minimal risk to a subject's rights and welfare, the requirement for consent may be waived if the practicability requirement is revised for this category of research.

NBAC believes that these interpretations and recommended changes in the regulations will allow important research to proceed while also considering potential harms to subjects. However, it must be noted that by dropping the requirement that consent must be obtained if practicable, NBAC does so with the expectation that the process and content of informed consent for the collection of new specimens will be explicit regarding the intentions of the subjects and the research use of their materials. (See Recommendations 6 through 9 concerning informed consent.)

Providing Additional Information as Required at 45 CFR 46.116(d)(4)

According to the current regulations, the fourth condition for the waiver of consent stipulates that "whenever appropriate, the subjects will be provided with additional pertinent information after participation" (45 CFR 46.116(d)(4)). The historical context for this condition is the use of "deception" studies (e.g., in the behavioral sciences) in which it is deemed crucial to the study design that the subjects be unaware of the details of the study design or, on occasion, that they are the subjects of the study. Thus, according to the regulations, an IRB, while waiving consent (by finding and documenting the first three required conditions), could require that subjects be informed that they are subjects of research and that they be provided details of the study—a so-called debriefing requirement.

The applicability of this condition in the context of stored samples could be interpreted in a variety of ways. If the first three conditions of waiver of consent are met, the IRB might require, as an additional measure of protection, that the investigator provide some information to the subjects. Such a communication would describe the status of the research project and inform them that their samples will be used or were used in the research. Such a requirement might be appropriate only if consent already had been obtained and the IRB determines that reconsent is not required for a specific or new protocol. The IRB might well recognize that only those subjects who could be found would be so informed.

Respect for subjects' rights and welfare in such circumstances will usually dictate that they be informed after-the-fact of the research in which they have been involved as naive or unwitting subjects and perhaps offered the opportunity to withdraw their information from the investigator's data. In general, however, NBAC concludes that this fourth criterion for waiver of consent is not relevant to research using human biological materials and, in fact, might be harmful if it forced investigators to recontact individuals who might not have been aware that their materials were being used in research.

Recommendation 13:
OPRR should make clear to investigators and IRBs that the fourth criterion for waiver, that "whenever appropriate, the subjects will be provided with additional pertinent information after participation" (45 CFR 46.116(d)(4)), usually does not apply to research using human biological materials.

"Opt Out" as an Additional Measure of Protection When the Consent Requirement Has Been Waived

"Opt out" refers to the choice given to sources to exclude themselves from a study. Unless someone has "opted out," he or she is assumed to be enrolled. If, after a waiver of the consent requirement is granted, an investigator or IRB has residual concerns regarding the nature of the research or the possibility that some individuals might find the research objectionable, then an additional measure may be taken to allow subjects to opt out of the research. In this scenario, subjects would, if possible, be contacted and given the choice of opting out; if they did not respond or could not be found, the sample still could be used because the consent requirement already would have been waived. This differs significantly from a scenario in which the consent requirement has not been waived. In such a scenario, if a person did not respond with explicit consent or could not be located, his or her sample could not be used in the research protocol.

Rendering Existing Identifiable Samples Unidentifiable to Avoid the Need for Consent

A more practical solution to using existing samples for which it is impracticable or problematic to gain express

informed consent for their specific uses is to render the samples unidentifiable. The rationale for this apparently simple proposal is that in many cases existing specimens were collected without anything close to adequate disclosure that they would be used for a range of purposes unrelated to the context in which they were collected.

Several drawbacks to rendering existing materials unidentifiable for every use that is not specifically consented to by the source should be noted. First, the administrative cost of rendering such materials completely unidentifiable would be high. Second, if a sample is not identifiable, opportunities may be lost to protect the well-being of the source or of his or her relatives (e.g., in the case of genetic conditions) when later research discovers therapeutically significant links between various diseases or between diseases and genotypes. Third, rendering a sample unidentifiable restricts the usefulness of that sample to investigators, who may wish to obtain additional samples or who may wish to gather additional medical information from the patient or the medical record. Thus, there could be a scientific or medical price to pay for this action. A possible ethical objection to this practice is based on the belief that rendering existing samples unidentifiable without consent is problematic because researchers once had the opportunity to seek consent but did not do so. Fourth, some investigators may choose to render identifiable samples unidentifiable in order to avoid the time and cost of IRB review and the possibility that the IRB might require informed consent.

NBAC believes that rendering existing samples unidentifiable in order to expedite research protocols may be avoided in many situations by designing the research in such a way that risks to the subjects are minimized. If risks are minimal, then it is possible that the requirement for informed consent might be waived or altered according to the regulations, 45 CFR 46.116(d). If the nature of the research changes in the future—so that an investigator now selects specific samples for additional studies that might increase risks beyond the minimal level—further IRB review would be required. Moreover, for future sample collection, a consent process that explicitly spells out the subject's wishes concerning uses of tissue will help to alleviate the investigator's need to use unidentified or unlinked samples.

Nevertheless, NBAC recognizes that some situations will occur in which it is scientifically sound or desirable to render samples unidentifiable through unlinking and that there is little or no scientific or medical cost to doing so. In addition, NBAC understands that recontacting sources to seek consent could be costly and time consuming in situations in which there is little possibility for stigmatization or harm once the identifiers are removed. Furthermore, sample sources may not want to be contacted, and the process may be disruptive to them. With these considerations in mind, NBAC concludes that, in those circumstances in which valuable samples could not otherwise be used, in which consent would be difficult to obtain, and in which there is little or no scientific cost to losing the link, it is ethically acceptable to render samples unidentifiable without the source's consent. In arriving at this conclusion, NBAC also considered input from the public that was received during its deliberations. Most citizens emphasized in their comments that they did not view their donated biological materials as something that belonged to them, but rather as a gift to be used by the scientific community, one that would be subject to review for quality and ethical acceptability and one that would be made if they could be assured that the information obtained would not be used to discriminate against them.

Reporting Research Results to Subjects

Experts disagree about whether findings from research should be communicated to subjects, although most do believe that findings should not be conveyed unless they are confirmed and reliable and constitute clinically significant or scientifically relevant information. Those who oppose revealing unconfirmed findings argue that the harms that could result from revealing preliminary data are serious, including anxiety or unnecessary (and possibly harmful) medical interventions. They prefer to avoid such harms by controlling the flow of information to subjects and by limiting communications to those that constitute reliable information. MacKay, writing about the development of genetic tests, contends that preliminary results do not yet constitute "information" since "until an initial finding is confirmed, there is no reliable information" to communicate to subjects, and that "even…confirmed findings may have some unforeseen limitations"

(1984). Subjects should not be given information about their individual test results until the findings have been confirmed through the "development of a reliable, accurate, safe and valid presymptomatic test" (MacKay 1984; Fost and Farrell 1989). Others have argued that the principle of autonomy dictates that subjects have a right to know what has been learned about them, and that therefore, interim results should be shared with subjects (Veatch 1981).

Reilly suggests that IRBs should develop general policies governing the disclosure of information to subjects to help make these determinations. At the very least, the following three factors should be considered: "1) the magnitude of the threat posed to the subject; 2) the accuracy with which the data predict that the threat will be realized; and 3) the possibility that action can be taken to avoid or ameliorate the potential injury" (1980). IRBs should require investigators to define three categories of findings: 1) "findings that are of such potential importance to the subject that they must be disclosed immediately"; 2) "data that are of importance to subjects…but about which [the investigator] should exercise judgment about the decision to disclose…[i]n effect, these are data that trigger a duty to consider the question of disclosure"; and 3) "data that do not require special disclosure" (Reilly 1980).

Recommendation 14:
IRBs should develop general guidelines for the disclosure of the results of research to subjects and require investigators to address these issues explicitly in their research plans. In general, these guidelines should reflect the presumption that the disclosure of research results to subjects represents an exceptional circumstance. Such disclosure should occur only when all of the following apply:

a) the findings are scientifically valid and confirmed,
b) the findings have significant implications for the subject's health concerns, and
c) a course of action to ameliorate or treat these concerns is readily available.

Recommendation 15:
The investigator in his or her research protocol should describe anticipated research findings and circumstances that might lead to a decision to disclose the findings to a subject, as well as a plan for how to manage such a disclosure.

Recommendation 16:
When research results are disclosed to a subject, appropriate medical advice or referral should be provided.

Considerations of Potential Harms to Others

The federal regulations governing the protection of research subjects extend only to individuals who can be identified as the sources of the biological samples. The exclusive focus of the regulations on the individual research subject is arbitrary from an ethical standpoint, because persons other than the subject can benefit or be harmed as a consequence of the research.

Risks to Groups

Research on samples that implicates groups may place group members at risk of harm. For example, research revealing that a racial or ethnic group is prone to a particular disease could be used to stigmatize and discriminate against group members.

OPRR guidance to IRBs and investigators on how best to identify and minimize risks to groups is required. Consultation with group members before designing and implementing research on groups, for example, often may be an effective way to understand and reduce risks. However, additional work is needed to identify appropriate mechanisms for group consultation.

It also seems appropriate to highlight how some of these issues should be discussed among researchers and their professional organizations. For example, what is the appropriate role of public health policy in developing new knowledge from genetic epidemiology? Will additional ethical considerations be needed to ensure that the benefits of public health objectives do not come at the cost of individual concerns? For many studies, the answer to the latter question may be yes. The net gain to a particular population that results from being informed about its increased risk (especially when something can be done with this knowledge at an individual level) often will outweigh the harms that come from labeling the group as high risk.

Risks and Potential Benefits to Relatives of the Sample Source

Others who may be at some risk are first-degree relatives or next-of-kin of the source. The need to consider these individuals as at risk is particularly evident when the disease or condition being studied is genetic or involves infectious agents or toxins to which family members also may have been exposed. In these instances, investigators are likely to be aware that the research they are conducting on a sample might have implications for those closely related to the sample source—individuals who are readily identifiable.[12] NBAC does not assume that because there might be risks to relatives of the sample source, those risks warrant considering the relatives to be human subjects who deserve the protection of informed consent.[13] In fact, NBAC finds that the possibility that a relative of the source could terminate a research protocol on the basis that he or she also must give consent is not only impractical but troublesome. If the source has consented to the research use of his or her sample, that consent alone is sufficient for the research to proceed. However, although the regulations do not require that the concerns of first-degree relatives be considered, NBAC recognizes that there might be circumstances in which an investigator finds it useful, beneficial, appropriate, and feasible to consider potential harms and benefits applicable to such individuals.

A different set of concerns arises when the source of the sample is deceased. Under federal regulations, people are human subjects only while they are living. Research involving human biological materials from individuals who are deceased at the time of the research is not subject to the requirements of the Common Rule, regardless of whether or not prior informed consent was obtained. In addition, the existing regulations do not make explicit the status of living relatives of deceased individuals whose stored samples are used in research.[14] However, it is possible that the living relatives of the deceased sample source might have an interest in the research, particularly if the investigation has focused on hereditary traits.

Recommendation 17:
Research using stored human biological materials, even when not potentially harmful to individuals from whom the samples are taken, may be potentially harmful to groups associated with the individual. To the extent such potential harms can be anticipated, investigators should to the extent possible plan their research so as to minimize such harm and should consult, when appropriate, representatives of the relevant groups regarding study design. In addition, when research on unlinked samples that poses a significant risk of group harms is otherwise eligible for exemption from IRB review, the exemption should not be granted if IRB review might help the investigator to design the study in such a way as to avoid those harms.

Recommendation 18:
If it is anticipated that a specific research protocol poses a risk to a specific group, this risk should be disclosed during any required informed consent process.

Publication and Dissemination of Research Results

Publishing research results with identifiable information in scientific or medical journals and elsewhere may pose a risk to the privacy and confidentiality of research subjects. Public disclosure of such information through written descriptions or pedigrees may cause subjects to experience adverse psychosocial effects. In addition, without the informed consent of the individual, such disclosure infringes on the rights of the subject or patient. Because of the familial nature of information in pedigrees, their publication poses particularly difficult questions regarding consent. Investigators should be aware that the ways in which research results are publicized or disseminated can affect the privacy of human subjects. NBAC believes that the source of funding, i.e., public or private, should not be an important consideration in determining the ethical acceptability of the research.

Recommendation 19:
Investigators' plans for disseminating results of research on human biological materials should include, when appropriate, provisions to minimize the potential harms to individuals or associated groups.

In addition, journal editors have an ethical obligation to publish only human subjects research that they have reason to believe was conducted according to ethical standards set forth in the Common Rule, which includes

review by an IRB. Recent studies have reported that ethical standards communicated in journals' instructions to authors vary widely, as do authors' adherence to such standards.

Recommendation 20:
Journals should adopt the policy that the published results of research studies involving human subjects must specify whether the research was conducted in compliance with the requirements of the Common Rule. This policy should extend to all human subjects research, including studies that are privately funded or are otherwise exempt from these requirements.

Professional Education and Responsibilities

Public and professional education plays an essential role in developing and implementing effective public policy regarding the use of human biological materials for research. By education, NBAC is referring not simply to the provision of information with the aim of adding to the net store of knowledge by any one person or group; rather, education refers to the ongoing effort to inform, challenge, and engage. Providing education regarding ethical issues in research that involves human biological materials would mean that a variety of individuals and groups would gain new tools with which to assess these important issues. Therefore, opportunities for such education must be made available to IRBs, researchers, other members of the research and academic community, political decisionmakers at the state and federal levels, interest groups, possible human subjects, and the eventual consumers of research on human biological materials. In addition, widespread and continuing deliberation must occur regarding informing and educating the public about developments in the field of genetics and in other areas in the biomedical sciences, especially when they affect important cultural practices, values, and beliefs.

Recommendation 21:
NIH, professional societies, and health care organizations should continue and expand their efforts to train investigators about the ethical issues and regulations regarding research on human biological materials and to develop exemplary practices for resolving such issues.

NIH can promote these efforts through the use of workshops, conferences, requirements for training grants and center grants, and funding for research on pertinent topics related to this report, and professional societies can develop training materials on these issues and disseminate information about how research centers have addressed ethical issues regarding research on human biological materials successfully. In doing so, the development of consent processes that allow patients and research volunteers to make meaningful choices about how biological materials might be used in future research should be emphasized.

Continued collaborative efforts between scientists, patient representatives, and advocacy groups are likely to be particularly fruitful in strengthening the consent process. Discussions regarding this subject should encompass the types of ethical concerns raised by the storage and use of human biological materials and the importance of appropriate protection of human subjects whose materials are used in such research. Moreover, because it is the research community that seeks access to these materials, for policy purposes the moral burden should fall upon researchers to elicit from prospective contributors, both individuals and groups, the values and meaning that they attach to the requested samples.

Recommendation 22:
Compliance with the recommendations set forth in this report will require additional resources. All research sponsors (the government, private sector enterprises, and academic institutions) should work together to make these resources available.

Use of Medical Records in Research on Human Biological Materials

In recent years, attention increasingly has been paid by policymakers to the need to protect the health information of the individual. Extensive efforts at the state and federal levels to enact such protections have resulted in the setting of a variety of limitations on access to patients' medical records. NBAC notes that debates about medical privacy are relevant to researchers using human biological materials in two ways. First, these researchers often need access to patient medical records, either to identify

research sample sources or to gather accompanying clinical information. Such activities constitute human subjects research and should be treated accordingly. The recommendations contained in this report provide a model framework for considering research in which the human subject is defined through his or her biological material. Many of these recommendations could apply equally to research in which the human subject is defined through access to his or her medical record. Thus, policymakers, investigators, and IRBs considering medical records research could benefit from NBAC's work in the area of human biological materials research.

Second, the development of statutes and regulations designed to protect the patient's medical record could have the unintended consequence of creating a dual system of protections—one for the medical record and one for human biological materials. Moreover, restricting access to the medical record could impede legitimate and appropriate access on the part of investigators whose protocols have undergone proper review.

Recommendation 23:
Because many of the same issues arise in the context of research on both medical records and human biological materials, when drafting medical records privacy laws, state and federal legislators should seek to harmonize rules governing both types of research. Such legislation, while seeking to protect patient confidentiality and autonomy, should also ensure that appropriate access for legitimate research purposes is maintained.

Differences in the rules governing research on medical records and human biological materials should be adopted only when it is critical to consider the important differences between the two types of research, including the fact that the information that may be found by studying cells and tissues differs in significant respects from the information that is found in medical records.

Summary

To advance human health, it is critical that human biological materials continue to be available to the biomedical research community. Increasingly, it will be essential for investigators to collect human biological materials from individuals who are willing to share important clinical information about themselves. In addition, it is crucial that the more than 282 million specimens already in storage remain accessible under appropriate conditions and with appropriate protections for the individuals who supplied this material.

The growing availability to third parties of genetic and other medical information about individuals has fueled the current debate about medical privacy and discrimination, and NBAC is sensitive to the possibility that the use of information obtained from human biological samples can lead to harms as well as benefits. These concerns require that those who agree to provide their DNA, cells, tissues, or organs for research purposes not be placed at risk. Measures to provide appropriate protections for individual privacy and for the confidentiality of clinical and research data are important if significant research is to continue. The recommendations provided in this report are intended to promote the goals of improving health through biomedical research while protecting the rights and welfare of those individuals who contribute to human knowledge through the gift of their biological materials.

Notes

1 King, M., "Genetics Research in Individuals, Families, and Communities." Testimony before NBAC. July 15, 1998. Portland, OR.

2 The protections provided by the Common Rule currently apply only to 1) research conducted or funded by one of the 17 agencies that have agreed to be subject to the Common Rule or by any other federal agency that has promulgated its own set of human subjects research rules, or 2) research conducted at an institution that has provided in its "Assurance" with the federal government that all research with human subjects conducted at the institution will be governed by the federal regulations whether or not the research is federally sponsored. In addition, the FDA regulates human subjects research involving an investigational new drug, device, or biologic.

3 45 CFR 46.102(f)(1) and (2).

4 See 45 CFR 46.102 (f). If the source of the sample is deceased, then, according to the regulations, there is no human subject, and the regulations do not apply. However, circumstances may exist in which research on samples of deceased individuals has implications for living relatives; if the findings were attached in some way to these relatives, they might be considered human subjects, which could trigger the federal regulations.

5 Personal communication from OPRR Director, Dr. Gary Ellis, August 25, 1998.

6 American Type Culture Collection, www.atcc.org/.

7 Moreover, some newer DNA databases (e.g., those associated with the federally funded Human Genome Project) are organized based on the assumption that such information should be available to any scientist wanting to investigate the basic structure or function of DNA. For example, the National Human Genome Research Institute implements a policy requiring that primary human genomic sequence data be rapidly released (within 24 hours of generation).

8 In reviewing the policies and procedures of several repositories, the Commission found that some require that investigators provide a statement of their research intent and an assurance of compliance with the Common Rule, but it is not clear that this practice is widespread, especially among smaller, more informal tissue collections.

9 Elsewhere, NBAC has discussed the issue of prospective authorization and found that under some circumstances it is an important method of respecting individual choices (NBAC 1998). NBAC does not regard prospective authorization alone as sufficient for enrollment in research, but recognizes its moral value and its use to communicate to appropriate decisionmakers the person's prior attitude about research participation.

10 NBAC Meeting. December 9, 1997. Arlington, VA.

11 Personal Communication, Dr. Gary Ellis, Director, OPRR, August 25, 1998.

12 This distinction is worth noting. In the case of membership in a group, persons might not be individually identifiable although identified as a member of that group. In the case of biological relatives, persons related to the sample source are likely to be individually identifiable (DeRenzo, Biesecker, and Meltzer 1997).

13 OPRR has indicated that the living relatives might in fact be considered human subjects by virtue of their genetic relationship to the sample source, but the regulations—specifically the *OPRR Institutional Review Board Guidebook* section on human genetic research (pp. 5–42 to 5–63)—do not clearly specify how this consideration is to be handled by IRBs.

14 45 CFR 46.102. "Definitions: (f) Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information...."

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Appendix A

Beliefs About the Research Use of Human Biological Materials

Background

The National Bioethics Advisory Commission (NBAC) believes that the opinions of members of the American public—those individuals who are neither medical researchers nor ethical experts—regarding the uses of stored human biological materials in research provide important additional information for consideration in its report and recommendations. Therefore, NBAC contracted with the Center for Health Policy Studies (CHPS) to gather a selection of members of the public in order to explore their knowledge, beliefs, and feelings about a variety of issues regarding human biological materials. This study is available in Volume II of this report. While the information gathered in the process of the study informed NBAC's discussions, the information reported here understandably is limited in its generalizability.

Study Purpose

This study was conducted in order to explore public knowledge, beliefs, and feelings about issues regarding human biological materials in six distinct areas of inquiry: consent and ownership; privacy and confidentiality; stigmatization of ethnic groups; third party concerns; sponsorship of research; and safeguards. More generally, CHPS conducted public discussion forums across the United States in order to obtain a sense of what the American public believes and feels about uses of human biological materials, about the ethical obligations of those who may learn significant health information from those materials, and about privacy protections. Forum locations included San Francisco, California; Miami, Florida; Honolulu, Hawaii; Mililani, Hawaii; Boston, Massachusetts; Cleveland, Ohio; and Richmond, Virginia.

Findings

Knowledge about Storage of Human Biological Materials

At the beginning of each forum and before the discussion of specific issues began, participants were asked a number of questions in order to assess their knowledge regarding the storage of human biological materials. Members of the discussion groups were asked to identify what body parts, organs, or tissues may be classified as human biological materials and ways in which such materials may be collected. Participants' knowledge regarding the use of these materials for research purposes also was assessed.

Across groups, participants generally understood what constitutes human biological materials and what these materials can reveal about people. However, most participants had never considered what happens to tissue specimens once they have been used for their initial purposes. Many believed that these samples are destroyed or discarded. One exception was a participant in the Honolulu forum who understood that tissue can be stored for later re-testing or comparison. Many participants stated that they had had tissue removed during a medical or surgical procedure, although not all of them recalled what issues were covered in the consent forms they had signed or even whether they had signed consent forms at all. Most who had signed consent forms were not sure whether the forms discussed the disposition of the tissue.

Beliefs and Attitudes about Storage of Human Biological Materials

The following sections present findings from the forums on public beliefs and attitudes regarding human biological materials. These findings include participants' responses to hypothetical scenarios regarding issues pertaining to ownership and consent; privacy and confidentiality; stigmatization of ethnic groups; third party concerns; sponsorship of research; and safeguards for research.

Ownership and Consent

Regarding ownership, many participants believed that if consent was provided for a procedure during which tissue was removed from a patient's body, the hospital or provider would own the tissue. A few believed that the individual from whom the material is taken should own the material. Participants in one of the Hawaii forums distinguished between ownership of the tissue by the hospital or the provider and ownership of the information that may be revealed by the material by the patient.

Participants also were asked whether specific consent should be obtained from patients to use samples for research and whether they would want to consent to each potential study of their tissues. Opinions varied across groups. Some participants stated that there is no need to specifically consent to research on stored specimens, especially if those specimens are anonymous. Other participants, particularly those in the Cleveland and Miami groups, believed they should provide consent for each potential study of their tissues. However, many felt that a general, one-time consent (i.e., blanket consent) for research was sufficient.

Privacy and Confidentiality

Participants were asked to share their feelings about privacy rights and the importance of confidentiality. Issues concerning insurance companies' access to research results, linkages between identities and research, and potential threats to confidentiality were discussed. Most forum participants expressed the strong belief that insurance companies should not have access to the results of genetic research on stored tissue specimens.

Across groups, participants varied in their consideration of how to balance the advantages of conducting research on genetic diseases with the possible abuses of privacy that may occur during such research. In general, most participants expressed positive views about the value of medical research. Participants in the Hawaii forums and in the San Francisco forum were vocal about the importance of medical research and did not express concern about potential privacy abuses. Participants in Cleveland and Miami, however, did express concern about the protection of their privacy rights. Many participants across forum sites stated that they wanted to be notified if researchers later discovered medically useful information about them from stored specimens, although some participants in Cleveland disagreed and commented that their privacy was more important. Some participants in Boston believed that it is important to define what comprises "medically useful information," because they did not believe findings indicating a propensity to disease or risk of a genetic condition or disease met their criteria for notification. San Francisco participants felt strongly that their physicians, not researchers, should relay the results of research.

Most participants agreed that the use of anonymous specimens for research is acceptable and even necessary for the public good. Moreover, across groups, most participants were not concerned about the linkage of demographics (e.g., age, sex, ethnic group) with their stored specimens, although participants in Miami wanted to ensure that their privacy would be maintained. Opinions varied regarding the issue of linking identifying information with stored specimens. Most participants in Hawaii, San Francisco, and Miami felt that linked research is acceptable and appropriate. On the other hand, many participants in Cleveland and some in Boston did not want any links maintained between their stored specimens and their identities.

Across localities, participants expressed skepticism when asked to consider what would happen if the confidentiality of research findings was not maintained. They believed that privacy and confidentiality could not be ensured because of the sophistication and complexity of computer information systems and the general commercial health care environment.

Stigmatization of Ethnic Groups

Forum participants were asked to discuss how they felt about researchers studying specific groups of people,

such as particular ethnic or racial groups. Participants considered specifically whether such research potentially could stigmatize certain groups. Generally, participants across forums did not express concern that research could stigmatize specific groups; however, participants in most groups did mention that this research could result in negative effects, including the denial of insurance coverage for members of the groups being studied and the potential for the dissemination of research findings that might later be disproved. Participants in all groups believed that the groups being studied generally tend to benefit from such research, and they cited examples, such as research on Tay-Sachs disease and sickle cell disease.

Third-Party Concerns

Forum participants responded to a number of questions regarding genetic research in which one person's stored specimen could reveal certain information about his or her family members. Across forums, participants expressed mixed feelings about how and under what circumstances family members should be informed of such research. Many participants said that they would want to be informed of genetic research that revealed information about them. Some recognized, however, that many family members might not want to be privy to this information, and issues arose regarding who should inform family members of research results (e.g., physicians, researchers, or the individuals from whom the tissue was taken). When asked whether family members should be provided the opportunity to consent to a study of their relatives' tissue, most believed that this would be inappropriate and difficult to achieve. Across groups, most participants did not feel that negative consequences would result from studying diseases that tend to run in families.

Participants also were asked who should make decisions about specimen storage for those who are unable to make such decisions. Categorically, participants expressed the belief that legal guardians or medical surrogates should make these decisions, and some participants were vocal in stating that individuals' preferences should be considered whenever possible (e.g., for children).

Sponsorship of Research

Participants discussed how they felt about researchers accessing their stored specimens and whether the kind of organization sponsoring the research matters (i.e., a for-profit company, a university, or the federal government). Most participants believed that researchers in all of these kinds of organizations should be able to gain access to stored specimens, although a few stated that important differences among various kinds of research organizations do exist. Some participants in Cleveland, Boston, and Miami believed that the profit motives of biotechnology and pharmaceutical companies set the research they conduct apart from that conducted by academic institutions. However, most of the participants in Richmond, Mililani, and San Francisco believed that the various sponsors of research are not characterized by significant differences in this respect.

Across groups, many participants were not concerned about whether firms could profit from research on stored specimens. A few participants in the Boston and Miami forums did, however, express some discomfort regarding the profit motives of companies. Some participants in Honolulu and Miami indicated that they would want to share in any profits that might result from research on their stored specimens. Overall, however, most participants did not believe this was an important or practical concern.

Safeguards

Across localities, participants who were asked about issues related to safeguards for research and medical information felt that before conducting research on stored tissue specimens, researchers should be required to receive approval from a committee or other entity that oversees the ethics of research. When asked who should review and oversee this research, participants identified individuals who would typically comprise Institutional Review Boards. In addition, some stated that representatives of the groups studied and people with high ethical standards (regardless of profession) should be included. Participants could not, however, categorically identify a group that could be trusted to protect medical information.

Appendix B

Code of Federal Regulations, Title 45, Part 46

Subpart A: Federal Policy for the Protection of Human Subjects (Basic DHHS Policy for Protection of Human Research Subjects)

Source: 56 FR 28003, June 18, 1991.

§46.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any Federal Department or Agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by Federal civilian employees or military personnel, except that each Department or Agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States.

(1) Research that is conducted or supported by a Federal Department or Agency, whether or not it is regulated as defined in §46.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a Federal Department or Agency but is subject to regulation as defined in §46.102(e) must be reviewed and approved, in compliance with §46.101, §46.102, and §46.107 through §46.117 of this policy, by an Institutional Review Board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by Department or Agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:[1]

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research involving the collection or study of existing data, documents, records, pathological

specimens, or diagnostic specimens, if these sources are publicly available or 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.

(5) Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or Agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or Agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the Department or Agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent Federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any State or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a Department or Agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the Department or Agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the Department or Agency head, notices of these actions as they occur will be published in the Federal Register or will be otherwise published as provided in Department or Agency procedures.

(i) Unless otherwise required by law, Department or Agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes or research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the Department or Agency head shall forward advance notices of these actions to the Office for Protection from Research Risks, National Institutes of Health, Department of Health and Human Services (DHHS), and shall also publish them in the Federal Register or in such other manner as provided in Department or Agency procedures.[1]

[1] Institutions with DHHS-approved assurances on file will abide by provisions of Title 45 CFR Part 46 Subparts A-D. Some of the other departments and agencies have incorporated all provisions of Title 45 CFR Part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, Subparts B and C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, Subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

§46.102 Definitions.

(a) *Department or Agency* head means the head of any Federal Department or Agency and any other officer or employee of any Department or Agency to whom authority has been delegated.

(b) *Institution* means any public or private entity or Agency (including Federal, State, and other agencies).

(c) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

(e) *Research subject to regulation*, and similar terms are intended to encompass those research activities for which a Federal Department or Agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a Federal Department or Agency solely as part of the Department's or Agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) data through intervention or interaction with the individual, or

(2) identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) *IRB* means an Institutional Review Board established in accord with and for the purposes expressed in this policy.

(h) *IRB approval* means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

(i) *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.

(j) *Certification* means the official notification by the institution to the supporting Department or Agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

§46.103 Assuring compliance with this policy —research conducted or supported by any Federal Department or Agency.

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a Federal Department or Agency shall provide written assurance satisfactory to the Department or Agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual Department or Agency heads shall accept the

existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, National Institutes Health, DHHS, and approved for Federal wide use by that office. When the existence of a DHHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to Department and Agency heads shall also be made to the Office for Protection from Research Risks, National Institutes of Health, DHHS.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the Department or Agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to Federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to Department- or Agency-supported or regulated research and need not be applicable to any research exempted or waived under §46.101 (b) or (i).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the Department or Agency head, unless in accord with §46.103(a) of this policy, the existence of a DHHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, National Institutes of Health, DHHS.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the Department or Agency head prescribes.

(d) The Department or Agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the Department or Agency and such experts or consultants engaged for this purpose as the Department or

Agency head determines to be appropriate. The Department or Agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the Department or Agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The Department or Agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a Federal Department or Agency and not otherwise exempted or waived under §46.101 (b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by §46.103 of this policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the Department or Agency to which the application or proposal is submitted. Under no condition shall research covered by §46.103 of the policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the Department or Agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

(Approved by the Office of Management and Budget under Control Number 9999-0020.)

§§46.104—46.106 [Reserved]

§46.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§46.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in §46.103(b)(4) and to the extent required by §46.103(b)(5).

(b) Except when an expedited review procedure is used (see §46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting

§46.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §46.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

(Approved by the Office of Management and Budget under Control Number 9999-0020.)

§46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the Federal Register. A copy of the list is available from the Office for Protection from Research Risks, National Institutes of Health, DHHS, Bethesda, Maryland 20892.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in §46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Department or Agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

§46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§46.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§46.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Department or Agency head.

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§46.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the Department or Agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

§46.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described in §46.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in §46.103(b)(4) and §46.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by §46.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the Department or Agency at reasonable times and in a reasonable manner.

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§46.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. 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.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) a description of any reasonably foreseeable risks or discomforts to the subject;

(3) a description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) additional elements of informed consent. When appropriate, one or more of the following elements

of information shall also be provided to each subject:

(1) a statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) any additional costs to the subject that may result from participation in the research;

(4) the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) the approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) the research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) the research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) the research involves no more than minimal risk to the subjects;

(2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) the research could not practicably be carried out without the waiver or alteration; and

(4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State, or local law.

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§46.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by §46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative.

Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(Approved by the Office of Management and Budget under Control Number 9999-0020.)

§46.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under §46.101 (b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the Department or Agency.

§46.119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the Department or Agency, and final approval given to the proposed change by the Department or Agency.

§46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

(a) The Department or Agency head will evaluate all applications and proposals involving human subjects submitted to the Department or Agency through such officers and employees of the Department or Agency and such experts and consultants as the Department or Agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the Department or Agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§46.121 [Reserved]

§46.122 Use of Federal funds.

Federal funds administered by a Department or Agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§46.123 Early termination of research support: Evaluation of applications and proposals.

(a) The Department or Agency head may require that Department or Agency support for any project be terminated or suspended in the manner prescribed

in applicable program requirements, when the Department or Agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the Department or Agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the Department or Agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to Federal regulation).

§46.124 Conditions.

With respect to any research project or any class of research projects the Department or Agency head may impose additional conditions prior to or at the time of approval when in the judgment of the Department or Agency head additional conditions are necessary for the protection of human subjects.

Subpart B: Additional DHHS Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization

Source: 40 FR 33528, Aug. 8, 1975; 43 FR 1758, January 11, 1978; 43 FR 51559, November 3, 1978.

§46.201 Applicability.

(a) The regulations in this subpart are applicable to all Department of Health and Human Services grants and contracts supporting research, development, and related activities involving: (1) the fetus, (2) pregnant women, and (3) human *in vitro* fertilization.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.202 Purpose.

It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable to assure that they conform to appropriate ethical standards and relate to important societal needs.

§46.203 Definitions.

As used in this subpart:

(a) "Secretary" means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services (DHHS) to whom authority has been delegated.

(b) "Pregnancy" encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.

(c) "Fetus" means the product of conception from the time of implantation (as evidenced by any of the presumptive signs of pregnancy, such as missed menses, or a medically acceptable pregnancy test), until a determination is made, following expulsion or extraction of the fetus, that it is viable.

(d) "Viable" as it pertains to the fetus means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the Federal Register guidelines to assist in determining whether a fetus is viable for purposes of this subpart. If a fetus is viable after delivery, it is a premature infant.

(e) "Nonviable fetus" means a fetus *ex utero* which, although living, is not viable.

(f) "Dead fetus" means a fetus *ex utero* which exhibits neither heart beat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached).

(g) "*In vitro* fertilization" means any fertilization of human ova which occurs outside the body of a

female, either through admixture of donor human sperm and ova or by any other means.

§46.204 Ethical Advisory Boards.

(a) One or more Ethical Advisory Boards shall be established by the Secretary. Members of these Board(s) shall be so selected that the Board(s) will be competent to deal with medical, legal, social, ethical, and related issues and may include, for example, research scientists, physicians, psychologists, sociologists, educators, lawyers, and ethicists, as well as representatives of the general public. No Board member may be a regular, full-time employee of the Department of Health and Human Services.

(b) At the request of the Secretary, the Ethical Advisory Board shall render advice consistent with the policies and requirements of this part as to ethical issues, involving activities covered by this subpart, raised by individual applications or proposals. In addition, upon request by the Secretary, the Board shall render advice as to classes of applications or proposals and general policies, guidelines, and procedures.

(c) A Board may establish, with the approval of the Secretary, classes of applications or proposals which: (1) must be submitted to the Board, or (2) need not be submitted to the Board. Where the Board so establishes a class of applications or proposals which must be submitted, no application or proposal within the class may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Board and the Board has rendered advice as to its acceptability from an ethical standpoint.

(d) *[Nullified under Public Law 103-43, June 10, 1993]*

§46.205 Additional duties of the Institutional Review Boards in connection with activities involving fetuses, pregnant women, or human in vitro fertilization.

(a) In addition to the responsibilities prescribed for Institutional Review Boards under Subpart A of this part, the applicant's or offeror's Board shall, with respect to activities covered by this subpart, carry out the following additional duties:

(1) determine that all aspects of the activity meet the requirements of this subpart;

(2) determine that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision has been made by the applicant or offeror for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the Institutional Review Board or subject advocates in: (i) overseeing the actual process by which individual consents required by this subpart are secured either by approving induction of each individual into the activity or verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and (ii) monitoring the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen);

(3) carry out such other responsibilities as may be assigned by the Secretary.

(b) No award may be issued until the applicant or offeror has certified to the Secretary that the Institutional Review Board has made the determinations required under paragraph (a) of this section and the Secretary has approved these determinations, as provided in §46.120 of Subpart A of this part.

(c) Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an Institutional Review Board, subject to approval by the Secretary, where no such Board has been established under Subpart A of this part.

§46.206 General limitations.

(a) No activity to which this subpart is applicable may be undertaken unless:

(1) appropriate studies on animals and nonpregnant individuals have been completed;

(2) except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity;

(3) individuals engaged in the activity will have no part in: (i) any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy; and

(4) no procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

(b) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

Source: 40 FR 33528, Aug. 8, 1975, as amended at 40 FR 51638, Nov. 6, 1975.

§46.207 Activities directed toward pregnant women as subjects.

(a) No pregnant woman may be involved as a subject in an activity covered by this subpart unless: (1) the purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if: (1) the purpose of the activity is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape.

§46.208 Activities directed toward fetuses *in utero* as subjects.

(a) No fetus *in utero* may be involved as a subject in any activity covered by this subpart unless: (1) the purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if: (1) his identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

§46.209 Activities directed toward fetuses *ex utero*, including nonviable fetuses, as subjects.

(a) Until it has been ascertained whether or not a fetus *ex utero* is viable, a fetus *ex utero* may not be involved as a subject in an activity covered by this subpart unless:

(1) there will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or

(2) the purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

(b) No nonviable fetus may be involved as a subject in an activity covered by this subpart unless:

(1) vital functions of the fetus will not be artificially maintained,

(2) experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and

(3) the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(c) In the event the fetus *ex utero* is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part.

(d) An activity permitted under paragraph (a) or (b) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) his

identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

§46.210 Activities involving the dead fetus, fetal material, or the placenta.

Activities involving the dead fetus, mascerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable State or local laws regarding such activities.

§46.211 Modification or waiver of specific requirements.

Upon the request of an applicant or offeror (with the approval of its Institutional Review Board), the Secretary may modify or waive specific requirements of this subpart, with the approval of the Ethical Advisory Board after such opportunity for public comment as the Ethical Advisory Board considers appropriate in the particular instance. In making such decisions, the Secretary will consider whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant such modification or waiver and that such benefits cannot be gained except through a modification or waiver. Any such modifications or waivers will be published as notices in the Federal Register.

Subpart C: Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Source: 43 FR 53655, Nov. 16, 1978.

§46.301 Applicability.

(a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.302 Purpose.

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

§46.303 Definitions.

As used in this subpart:

(a) "Secretary" means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) "DHHS" means the Department of Health and Human Services.

(c) "Prisoner" means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

(d) "Minimal risk" is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

§46.304 Composition of Institutional Review Boards where prisoners are involved.

In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.

(b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity,

except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

§46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

(1) the research under review represents one of the categories of research permissible under §46.306(a)(2);

(2) any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

(3) the risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;

(4) procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

(5) the information is presented in language which is understandable to the subject population;

(6) adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

(7) where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

(b) The Board shall carry out such other duties as may be assigned by the Secretary.

(c) The institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

§46.306 Permitted research involving prisoners.

(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:

(1) the institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under §46.305 of this subpart; and

(2) in the judgment of the Secretary the proposed research involves solely the following:

(A) study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(B) study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(C) research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research; or

(D) research on practices, both innovative

and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of the intent to approve such research.

(b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Subpart D: Additional DHHS Protections for Children Involved as Subjects in Research

Source: 48 FR 9818, March 8, 1983; 56 FR 28032, June 18, 1991.

§46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (i) of §46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of Subpart A are applicable to this subpart.

§46.402 Definitions.

The definitions in §46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) "Children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

(b) "Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) "Permission" means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) "Parent" means a child's biological or adoptive parent.

(e) "Guardian" means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

§46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§46.404 Research not involving greater than minimal risk.

DHHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in

§46.408.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) the risk is justified by the anticipated benefit to the subjects;

(b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) the risk represents a minor increase over minimal risk;

(b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

DHHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

(a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or (2) the following:

(i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) the research will be conducted in accordance with sound ethical principles;

(iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

§46.408 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they

cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A.

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by §46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §46.406 and §46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in §46.116 of Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, State, or local law. The choice of anappropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by §46.117 of Subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§46.409 Wards.

(a) Children who are wards of the State or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:

(1) related to their status as wards; or

(2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research,

Appendix C

Comparison Table of Professional Statements

Organization	Protections for Permissible Use of Existing Materials			Protections for Future Material Collection		
	Anonymous	Identifiable		Anonymous	Identifiable	
		Coded	Directly Identified		Coded	Directly Identified
American Association of Medical Colleges 1997	Policy statement speaks only to future use. **Informed consent:** Statement not explicit **IRB review:** Statement not explicit			**Informed consent:** YES General consent **IRB review:** Statement not explicit	**Informed consent:** YES General consent **IRB review:** Statement not explicit	**Informed consent:** YES Specific **IRB review:** Statement not explicit
American College of Medical Genetics 1995	**Informed consent:** "The following factors, among others, should be considered in deciding whether it is appropriate to use previously collected samples without contacting the individual: ■ are or will the samples be made anonymous?; ■ the degree to which the burden of contacting individuals may make it impracticable to conduct research; ■ existence and content of prior consent; and ■ risks and benefits." **IRB review:** Statement not explicit			**Informed consent:** YES for all above categories Consent for use of all clinical and research samples. **IRB review:** Statement not explicit		
American Society of Human Genetics 1996	**Informed consent:** "Not applicable" **IRB review:** Statement not explicit	**Informed consent:** YES[1] **IRB review:** Statement not explicit	**Informed consent:** YES **IRB review:** Statement not explicit	**Informed consent:** NO **IRB review:** Statement not explicit	**Informed consent:** YES - Layered **IRB review:** Statement not explicit	**Informed consent:** YES - Layered **IRB review:** Statement not explicit
Biotechnology Industry Organization 1997	**Informed consent:** NO **IRB review:** Statement not explicit	**Informed consent:** NO[2] **IRB review:** Statement not explicit	**Informed consent:** YES **IRB review:** Statement not explicit	**Informed consent:** Statement not explicit **IRB review:** Statement not explicit		

Organization	Protections for Permissible Use of Existing Materials			Protections for Future Material Collection		
	Anonymous	Identifiable		Anonymous	Identifiable	
		Coded	Directly Identified		Coded	Directly Identified
College of American Pathologists 1997	**Informed consent:** Statement not explicit **IRB review:** YES	**Informed consent:** Statement not explicit **IRB review:** YES[3]	**Informed consent:** Statement not explicit **IRB review:** YES	**Informed consent:** YES General consent for research, teaching and quality control **IRB review:** YES	**Informed consent:** YES General consent for research, teaching and quality control **IRB review:** YES	**Informed consent:** YES May not identify individuals in publications without specific consent **IRB review:** YES
ELSI Working Group 1995	**Informed consent:** NO Informed consent may be considered if identifiers are to be removed from currently linkable samples **IRB review:** YES	**Informed consent:** YES[4] **IRB review:** YES		**Informed consent:** YES[5] **IRB review:** YES		
Department of Health and Human Services 1997	**Informed consent:** Statement not explicit **IRB review:** Statement not explicit	**Informed consent:** Generally requires informed consent **IRB review:** YES	**Informed consent:** Generally requires informed consent **IRB review:** YES	**Informed consent:** Statement not explicit **IRB review:** Statement not explicit		
Human Genome Organziation 1998	**Informed consent:** NO[6,7] **IRB review:** YES	**Informed consent:** YES (Clinical) NO (Research) **IRB review:** YES	**Informed consent:** YES **IRB review:** YES	**Informed consent:** YES **IRB review:** YES	**Informed consent:** YES **IRB review:** YES	**Informed consent:** YES **IRB review:** YES
U.S. National Center for Human Genome Research and U.S. Department of Energy 1996	**Informed consent:** YES Continue to use existing libraries for large-scale sequencing, only if IRB approval and consent for continued use are obtained and approval by the funding agency is granted. IRB may determine that recontact should be made by a third party. **IRB review:** YES			**Informed consent:** YES[8] **IRB review:** YES	Do not construct identifiable sample collections.	

Organization	Protections for Permissible Use of Existing Materials			Protections for Future Material Collection		
	Anonymous	Identifiable		Anonymous	Identifiable	
		Coded	Directly Identified		Coded	Directly Identified
National Heart, Lung, and Blood Institute 1997	**Informed consent:** Use of sample must not violate original consent **IRB review:** Statement not explicit	**Informed consent:** Use of sample must not violate original consent **IRB review:** YES	**Informed consent:** IRB must judge adequacy of previous consent[9] **IRB review:** YES	**Informed consent:** YES - Layered **IRB review:** Statement not explicit		
Office for Protection from Research Risks 1997	**Informed consent:** YES[10] **IRB review:** YES[11]			**Informed consent:** YES **IRB review:** YES		
Pathologists Consensus Statement Revised 1997	**Informed consent:** NO **IRB review:** NO (includes anonymized samples)	**Informed consent:** NO **IRB review:** NO	**Informed consent:** YES **IRB review:** Statement not explicit	**Informed consent:** YES General consent[12, 13] **IRB review:** NO	**Informed consent:** Statement not explicit IRBs should be permitted to have broader latitude to waive requirement for informed consent on coded samples. **IRB review:** NO Review of procedure	**Informed consent:** YES **IRB review:** Statement not explicit
PRIM&R/ARENA Tissue Banking Working Group 1997	Principles apply to prospective collection with the intent that pathologists will adapt them to apply to existing collections. **Informed consent:** Statement not explicit **IRB review:** Statement not explicit			**Informed consent:** YES for all above categories **IRB review:** YES for all above categories		
Trans-NIH Bioethics Subcommittee 1993	**Informed consent:** Statement not explicit **IRB review:** Statement not explicit	**Informed consent:** Generally requires informed consent **IRB review:** YES	**Informed consent:** Generally requires informed consent **IRB review:** YES	**Informed consent:** Statement not explicit **IRB review:** Statement not explicit		

Notes

1 “Waivers may be granted, although the waivers will be difficult to justify by the above criteria [45 CFR § 46.116] if identifiers are retained.”

2 “In the context of when to require informed consent, we recommend that the bill's provisions apply only to samples that are personally-identifiable, not to ones that are anonymous or encoded. We believe that it would burden the process without providing patients with additional protections if the informed consent provisions were to be required for the use of non-identifiable samples in research. As long as there is an appropriate 'firewall' between the data and identifiers, the use of the data for further research should not breach confidentiality.”

3 “Each institution that controls or uses specimens of human tissue should have and enforce a written policy on confidentiality. For issues involving research, this policy should be approved by an institutional review board. Institutions should strive to maintain separation of information—that is, keeping patient identity and clinical information separate from research data through means such as coding.”

4 “Before requiring recontact: IRB determines if proposed research was agreed to at time of original sample collection. Implied consent sufficient. No consent if conditions for waiver are met under 45 CFR § 46.116.”

5 “Obtain informed consent for all samples likely to be used for research in the future. Present options of whether samples can be

1. linked and whether they want to be recontacted with results (should inform them about benefits and risks, confidentiality and ability to withdraw from studies);
2. stripped of identifiers;
3. shared with other investigators, whether linked or anonymous; or
4. used to study certain classes of diseases.”

6 “Routine samples obtained during medical care and stored may be used for research if there is general notification of such a policy, the patient has not objected, and the sample to be used by the researcher has been coded or anonymized. Routine samples obtained during medical care and stored before such notification of such a policy may be used for research if the sample has been anonymized prior to use.…”

7 “Research samples obtained with consent and stored may be used for other research if there is general notification of such a policy, the participant has not yet objected, and the sample to be used by the researcher has been coded or anonymized. For the use of research samples obtained before notification of a policy, these samples may be used for other research if the sample has been coded or anonymized prior to use.”

8 “In addition, there are several other disclosures that are of special importance for donors of DNA for large-scale sequencing. These include:

- The meaning of confidentiality and privacy of information in the context of large-scale DNA sequencing, and how these issues will be addressed;
- The lack of opportunity for the donor to later withdraw the libraries made from his/her DNA or his/her DNA sequence information from public use;
- The absence of opportunity for information of clinical relevance to be provided to the donor or his/her family;
- The possibility of unforeseen risks; and
- The possible extension of risk to family members of the donor or to any group or community of interest (e.g., gender, race, ethnicity) to which a donor might belong.”

9 In judging the adequacy of a previous informed consent, IRBs and funding agencies should consider “1. The nature of the proposed study, 2. The likelihood that knowing results of the research will harm or benefit individual, 3. The availability of effective treatment or prevention for the disorder, and 4. The burden of such treatment.”

10 Regarding the submittal of materials to the repository: “A written submittal agreement for tissue collectors should require written informed consent of the donor-subjects.…It should also contain an acknowledgment that collectors are prohibited from providing recipient-investigators with access to the identities of donor-subjects or to information through which the identities of donor-subjects may readily be ascertained.”

11 “A written usage agreement for recipient-investigators should include the following: 'Recipient acknowledges that the conditions for use of this research material are governed by the cell repository Institutional Review Board (IRB) in accordance with Department of Health and Human Services regulations at 45 CFR 46.'”

12 “To give a description of each and every research protocol which might be performed in the (sometimes distant) future on a patient's tissue is an unreasonable burden for the patient and the researcher.…Provided that written nondisclosure, confidentiality, and security policies have been IRB-approved…we recommend that the appropriate regulatory agencies modify the current Federal regulations so that simple consent for research should be sufficient for the use of all samples that are anonymous or anonymized.”

13 “Specific informed consent must be obtained from the donor when specimens are collected specifically for research.”

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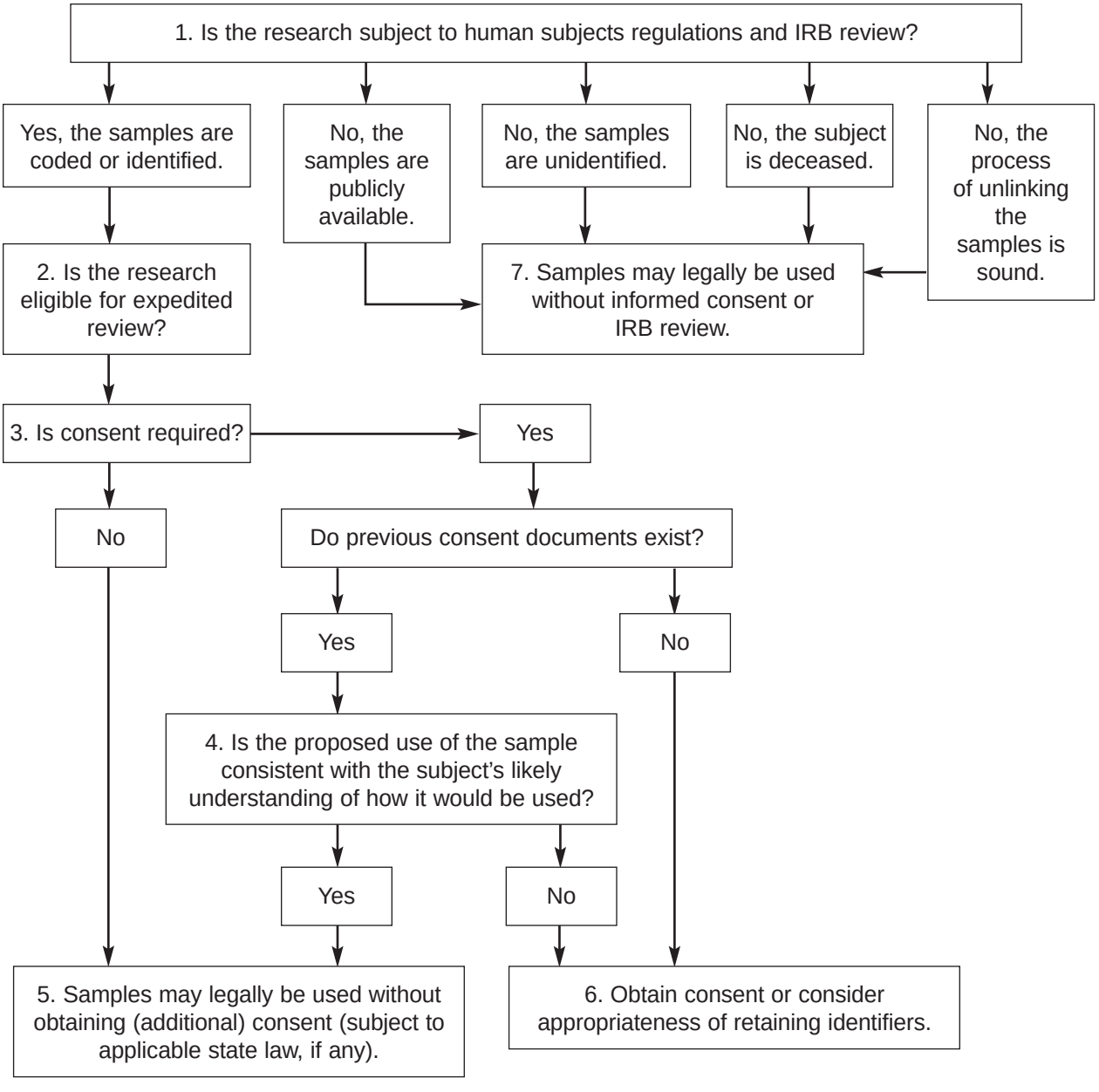
Appendix D

Guidance for Institutional Review Boards Reviewing Research Using Human Biological Materials

- NBAC's Proposed Process for Research Using Human Biological Materials
- Human Subject as Currently Defined by OPRR
- IRB Review for Research with Human Biological Materials
- NBAC's Proposed Informed Consent Requirements for Research with Human Biological Materials

Chart 1: NBAC's Proposed Process for Research Using Human Biological Materials

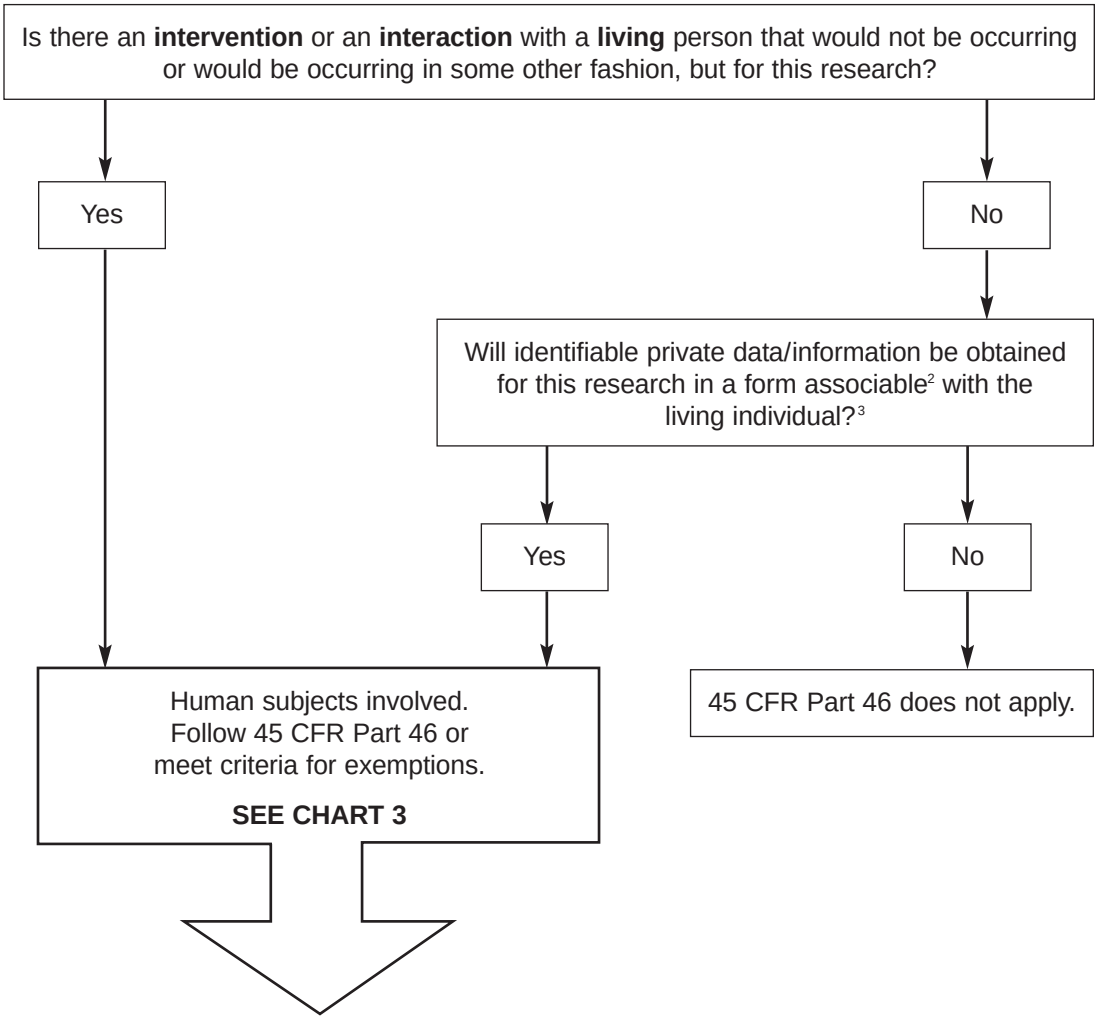


Key to Guidance in the Report

1) Is the research subject to human subjects regulations and IRB review? See Recommendations 1, 3, 4, and 5.
2) Is the research eligible for expedited review? See Recommendation 2.
3) Is consent required? See Recommendations 10, 11, 12, and 13.
4) Is the proposed use of the sample consistent with the subject's likely understanding of how it would be used? See Recommendations 6, 7, 8, 9, and 18. See Recommendations 14, 15, and 16 for disclosure of research results to subjects.
5) Samples may legally be used without obtaining (additional) consent (subject to applicable state law, if any). See Recommendations 19–23.
6) Obtain consent or consider appropriateness of retaining identifiers. See Recommendations 3, 6, 7, 8, 9, and 18.

Chart 2: Human Subject as Currently Defined by OPRR[1]

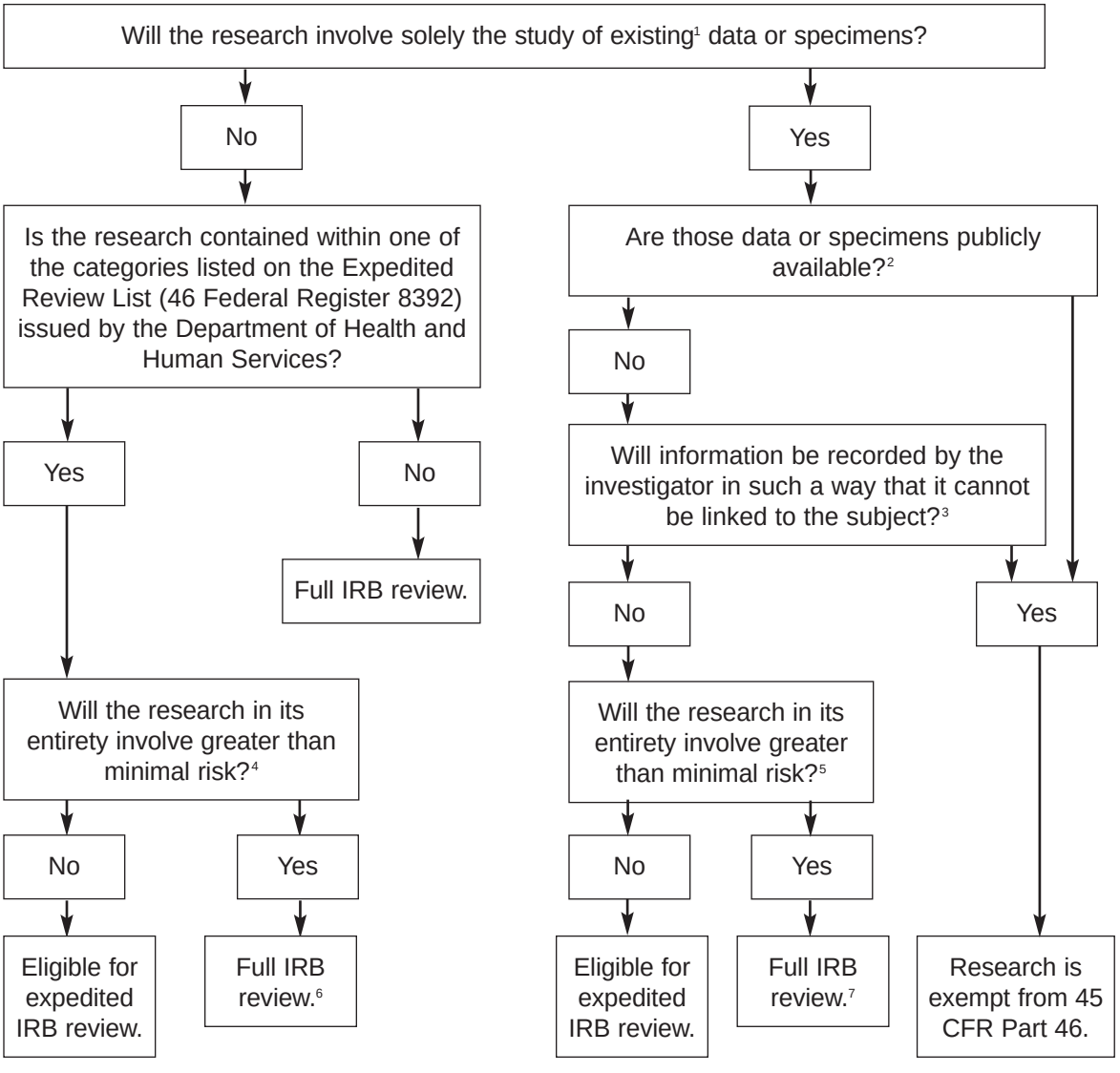
Is the definition of "human subject" at Section 46.102 (f) met in this research activity?



1 Adapted from Memorandum, Gary B. Ellis to Office for Protection from Research Risks (OPRR) Staff. April 17, 1996.
2 "That is, the identity of the subject is or may readily be ascertained or associated with the information." Ibid.
3 See Recommendation 1.

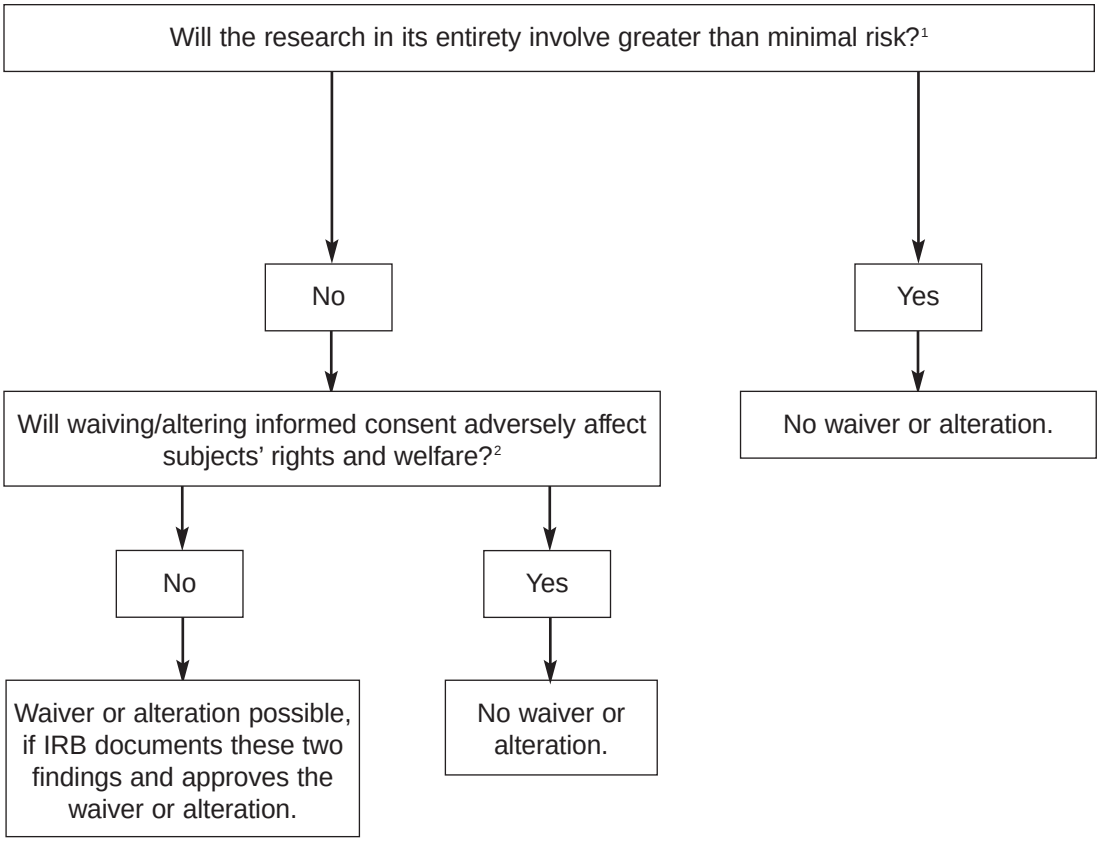
Chart 3: IRB Review for Research with Human Biological Materials

Guidelines for applying the exemption stated at 45 CFR 46.101(b)(4) and criteria for expedited review at §46.110.



1 "Existing" means collected (i.e., on the shelf) at the time the research is proposed. It includes data or specimens collected in research and nonresearch activities.
2 See Recommendation 1.
3 See Recommendations 1 and 3. This question is relevant to determine both (1) Is the definition of "human subject" at Section 46.102 (f) met in this research activity? and (2) Is the research exempt in accordance with Section 46.101 (b)(4)?
4 See Recommendations 2, 5, and 10.
5 See Recommendations 2, 5, and 10.
6 Research also is eligible for expedited IRB review if the subject of review involves exclusively minor changes in previously approved research during the period (of one year or less) for which approval is authorized.
7 See fn 6.

Chart 4: NBAC's Proposed Informed Consent Requirements for Research with Human Biological Materials[1]



1 See Recommendations 2, 5, and 10.
2 See Recommendations 11 and 12.

Appendix E

Public Comments on NBAC's February 22, 1999, Draft

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Caroline D. McCoy, Illinois State University (Bloomington, IL)

Jean E. McEwen, Boston College Law School (Newton, MA)

Elizabeth McPherson, Glaxo Wellcome, Inc. (Research Triangle Park, NC)

Jon F. Merz, University of Pennsylvania Center for Bioethics (Philadelphia, PA)

Marsel Mesulam, The Cognitive Neurology and Alzheimer's Disease Center, Northwestern University Medical School (Chicago, IL)

Abbey S. Meyers, National Organization for Rare Disorders (New Fairfield, CT)

Vincent M. Monnier, Case Western Reserve University (Cleveland, OH)

Donald E. Mosier, Department of Immunology, The Scripps Research Institute (La Jolla, CA)

Curtis R. Naser, Department of Philosophy, Fairfield University (Fairfield, CT)

Stuart L. Nightingale, Food and Drug Administration, Office of Health Affairs (Rockville, MD)

Ari Patrinos, Biology and Environmental Research, Department of Energy (Germantown, MD)

Carol K. Petito, Department of Pathology, University of Miami School of Medicine (Miami, FL)

Frances A. Pitlick, American Society for Investigative Pathology (Bethesda, MD)

Joan Porter, National Science and Technology Council (Washington, DC)

Rosalind Porter, National Community Advisory Board to the AIDS Vaccine Evaluation Group (Montgomery, AL)

Karen H. Rothenberg, University of Maryland School of Law (Baltimore, MD)

Marc A. Schuckit, Department of Psychiatry, San Diego Veterans Affairs Medical Center, University of California, San Diego School of Medicine (San Diego, CA)

James D. Shelton, U.S. Agency for International Development (Washington, DC)

Frank P. Simone, American Type Culture Collection (Manassas, VA)

Lana R. Skirboll, National Institutes of Health, Office of Science Policy (Bethesda, MD)

Mark E. Sobel, Association for Molecular Pathology (Bethesda, MD)

Robert Sparkes, Department of Medicine, University of California (Los Angeles, CA)

Donald Stablein, The EMMES Corporation (Potomac, MD)

Clive R. Taylor, Association of Pathology Chairs, Department of Pathology, University of Southern California (Los Angeles, CA)

Suzanne P. Tomlinson, Biotechnology Industry Organization (Washington, DC)

Russell P. Tracy, University of Vermont, Laboratory for Clinical Biochemistry (Colchester, VT)

John Q. Trojanowski, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine (Philadelphia, PA)

David Wargowski, University of Wisconsin-Madison School of Medicine (Madison, WI)

Beverly Woodward, Brandeis University (Waltham, MA)

Gillian R. Woollett, Pharmaceutical Research and Manufacturers of America (Washington, DC)

Appendix F

Public and Expert Testimony

December 13, 1996 (Bethesda, MD)
Public:
George Gasparis, Office for Protection from Research Risks
Susan Pollin, Kennedy Institute of Ethics, Georgetown University

January 9–10, 1997 (Washington, DC)
Expert:
David Korn, American Association of Medical Colleges
Debra Saslow, Office on Women's Health, Department of Health and Human Services
Mark Guyer, National Center for Human Genome Research

March 5, 1997 (Bethesda, MD) – Genetics Subcommittee
Expert:
Dorothy Wertz, Shriver Center for Mental Retardation
Chuck Denk, Mathematica
Ronald Cole-Turner, Pittsburgh Theological Seminary
Public:
Mark Sobel, National Cancer Institute

July 14, 1997 (Bethesda, MD)
Expert:
Sheri Alpert, Office of the Privacy Advocate, Internal Revenue Service

September 18–19, 1997 (Bethesda, MD)
Expert:
Bartha M. Knoppers, University of Montréal
Elisa Eiseman, RAND Corporation
Courtney Campbell, Oregon State University
Public:
John Cavanaugh-O'Keefe, American Bioethics Advisory Commission, American Life League

October 19, 1997 (Bethesda, MD)
Expert:
Robert Weir, University of Iowa

November 23, 1997 (Bethesda, MD)
Expert:
Elisa Eiseman, RAND Corporation
James Wells, Center for Health Policy Studies
Sheri Alpert, Office of the Privacy Advocate, Internal Revenue Service
Robert Weir, University of Iowa
Mark Sobel, National Cancer Institute
Frances Pitlick, American Society for Investigative Pathology

December 9, 1997 (Arlington, VA)
Expert:
John Killen, National Institute of Allergy and Infectious Diseases

January 6–7, 1998 (Arlington, VA)
Expert:
Susan E. Old, National Heart, Lung, and Blood Institute
Patricia Barr, National Action Plan on Breast Cancer
Public:
Mark Sobel, National Cancer Institute

March 3–4, 1998 (McLean, VA)
Expert:
Lisa Brooks, National Human Genome Research Institute
Mark Guyer, National Human Genome Research Institute
Public:
Karen Rothenberg, University of Maryland

May 20, 1998 (Cleveland, OH)
Expert:
C. Christopher Hook, The Mayo Clinic

July 14–15, 1998 (Portland, OR)
Expert:
Allen Buchanan, University of Arizona
Frank C. Dukepoo, Northern Arizona University
Mary-Claire King, University of Washington
Public:
Ted Falk, Portland, OR

March 2–3, 1999 (Vienna, VA)
Expert:
John Fanning, Office of the Assistant Secretary for Planning and Evaluation, Department of Health and Human Services

Appendix G

Commissioned Papers

The following papers, prepared for the National Bioethics Advisory Commission, are available in Volume II of this report:

Privacy and the Analysis of Stored Tissues
Sheri Alpert
Alexandria, Virginia

An Ethical Framework for Biological Samples Policy
Allen Buchanan
University of Arizona

Research on Human Tissue: Religious Perspectives
Courtney S. Campbell
Oregon State University

Stored Tissue Samples: An Inventory of Sources in the United States
Elisa Eiseman
RAND Critical Technologies Institute

Control of DNA Samples and Information
Bartha Maria Knoppers, Marie Hirtle, Sébastien Lormeau, Claude M. Laberge, Michelle Laflamme
CRDP (Public Law Research Centre), Faculty of Law, Université de Montréal, Québec

Contribution of the Human Tissue Archive to the Advancement of Medical Knowledge and the Public Health
David Korn
Stanford University School of Medicine

The Ongoing Debate About Stored Tissue Samples, Research, and Informed Consent
Robert F. Weir
University of Iowa

Mini-Hearings on Tissue Samples and Informed Consent
James A. Wells
Center for Health Policy Studies