Chapter 4
Current Guidance on the Use of Human Biological Materials in Research

In the United States, the current landscape of rules, principles, and guidelines affecting the use of human biological samples in research includes existing federal regulations, state statutes governing privacy and research use of medical records, policies developed by domestic scientific and professional societies, and guidelines developed by other countries and international organizations.

When NBAC began to review the use of human biological materials in research, the work of a number of these organizations provided a very useful understanding of the range of positions that exist among those that have carefully considered this subject. This chapter describes the existing federal regulations (see also Appendix C), and how the concepts of IRB review and informed consent might be viewed when considering the ethical research use of human biological materials. It also describes the current status of the debate over privacy of medical information and outlines existing policies regarding research use of human biological materials developed by scientific and professional societies, both domestically and internationally.

A BRIEF HISTORY OF HUMAN SUBJECTS PROTECTIONS

The modern story of human subjects protections begins with the Nuremberg Code,

developed for the Nuremberg Military Tribunal as standards by which to judge the human experimentation conducted by the Nazis.[1] The Code captures many of what are now taken to be the basic principles governing the ethical conduct of research involving human subjects. The first provision of the Code states that ?the voluntary consent of the human subject is absolutely essential." Freely given consent to participation in research is thus the cornerstone of ethical experimentation involving human subjects. The Code goes on to provide the details implied by such a requirement: capacity to consent, freedom from coercion, and comprehension of the risks and benefits involved. Other provisions require the minimization of risk and harm, a favorable risk/benefit ratio, qualified investigators using appropriate research designs, and freedom for the subject to withdraw from that study at any time.[2] The Code makes no provision for waiver or omission of consent.

[1] Several excellent sources trace the history of human subjects research and the development of the IRB system as a mechanism for the protection of human subjects. An account of the history of human subjects research and the human subjects protection system in the United States can be found in David J. Rothman's *Strangers at the Bedside: A History of How Law and Bioethics Transformed Medical Decision Making* (Chapters 1-5 and Epilogue) and in Dennis Maloney's *Protection of Human Research Subjects*. Rothman details the abuses to which human subjects were exposed, culminating in Henry Beecher's 1966 article, "Ethics and Clinical Research," published in the *New England Journal of Medicine*, and ultimately contributing to the impetus for the first NIH and Food and Drug Administration regulations. Other equally useful sources include Robert J. Levine's *Ethics and Regulation of Clinical Research* (Chapter 14), Joan E. Sieber's *Planning Ethically Responsible Research*, Robert M. Veatch"s "Human Experimentation Committees: Professional or Representative?," and William J. Curran's "Government Regulation of the Use of Human Subjects in Medical Research: The Approaches of Two Federal Agencies."

[2] Similar recommendations were made by the World Medical Association in *Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects*, first adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, and subsequently revised by the 29th World Medical Assembly, Tokyo, Japan, 1975, the 35th World Medical Assembly, Venice, Italy; the 41st World Medical Assembly, Hong Kong, 1989; and the 48th General Assembly, Somerset West, Republic of South Africa, 1996. The Declaration of Helsinki further distinguishes therapeutic from nontherapeutic

In the United States, federal regulations protecting human subjects first became effective on May 30, 1974. Promulgated by the Department of Health, Education and Welfare (DHEW), those regulations raised to regulatory status the National Institutes of Health (NIH) Policies for the Protection of Human Subjects, which were first issued in 1966. The regulations established the Institutional Review Board (IRB) as one mechanism through which human subjects would be protected.

In July of 1974, the passage of the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In keeping with its charge, the Commission issued reports and recommendations identifying the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and suggested guidelines to ensure that research is conducted in accordance with those principles. The Commission also recommended DHEW administrative action to require that the guidelines apply to research conducted or supported by DHEW.

On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, which set forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles—respect for persons, beneficence, and justice—are now broadly accepted as the three

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research.

quintessential requirements for the ethical conduct of research involving human subjects. The *Belmont Report* also describes how these principles apply to the conduct of research. Specifically, the principle of respect for persons underlies the need to obtain informed consent; the principle of beneficence underlies the need to engage in a risk/benefit analysis and to minimize risks; and the principle of justice requires that subjects be fairly selected.

In 1981, in response to the National Commission's reports and recommendations, both the Department of Health and Human Services (DHHS, formerly DHEW) and the U.S. Food and Drug Administration (FDA) promulgated significant revisions of their human subjects regulations. The revisions did not alter the general principles of IRB review as they had evolved over the preceding three decades. Rather, they focused on the details of what the IRB is expected to accomplish and some of the procedures it must follow (Levine, 1986, p. 324).

These "basic" regulations became final January 16, 1981, and were revised effective March 4, 1983, and June 18, 1991. The June 18, 1991, revision involved the adoption of the Federal Policy for the Protection of Human Subjects. The Federal Policy (or "Common Rule" as it is sometimes called) was promulgated by 17 federal agencies that conduct, support, or otherwise regulate human subjects research; the FDA also adopted certain provisions of the Common Rule. As is implied by its title, 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 NIH Office for Protection from Research Risks (OPRR) that has taken the lead within the Federal Government on the task of harmonizing human subjects protections across agencies.[3]

THE SCOPE OF THE CURRENT FEDERAL REGULATIONS

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

1. Is the research subject to federal regulation?

The federal regulatory protections only apply to: 1) research supported by funding from

[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.

one of the federal agencies subscribing to the Common Rule; 2) research on an investigational new drug, device or biologic subject to FDA rules; or 3) research conducted at an institution or by an individual investigator at that institution that has executed an assurance with the Federal Government stating that even research not otherwise covered by the regulations will nonetheless be governed by them.

For example, an investigator performing privately funded research at a large university that has executed a "multiple project assurance" with the Federal Government almost always will be required to abide by the federal regulations.[4] In addition, many multiple project assurance agreements include a provision that prevents researchers at that institution from evading federal regulation by conducting the research off-site or with a private, unregulated company. Instead, these multiple assurances typically promise that any researcher affiliated with the institution will abide by the federal regulations no matter where or with whom they work.

Thus, research on stored human biological materials carried out using private funding, using only investigators who are free of affiliations with institutions that have executed a multiple project assurance, might not be subject to the federal human subjects regulations.

2. Does the activity constitute research?

[4] The regulations require that each covered institution engaged in the conduct of research involving human subjects provide a written assurance of compliance, 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

The regulations do not apply to purely clinical interventions, even if they are experimental in nature. Rather, they apply to research, defined as "a systematic investigation designed to develop or contribute to generalizable knowledge" (46.102(d)). If the work on the stored materials is done solely as a part of clinical intervention, as might be the case in a pathology laboratory, then the federal regulations do not apply.

Work that has both a clinical and a research component, however, is covered by the federal regulations. Thus, if a pathology laboratory saves some tissue left over from a clinical intervention in order to do further, research-oriented testing that research would be subject to the federal regulations.

3. Does the research involve a "human subject"?

"Human subject" is defined by the regulations 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" (46.102(f)(1)&(2)). 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

assurance of compliance to OPRR the document is called an Agreement.

> 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.

From this definition it is apparent that an investigator who interacts with a person in order to obtain a new blood or saliva sample is doing 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 doing 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 specimens with codes that, with the cooperation of others, could be broken open in order to reveal the name of the tissue source.[5] On the other hand, according to the regulations, research on specimens provided to the investigator with no personal identifiers and where no codes linked to personal identifiers is maintained would not be covered by the regulations because no human subject would be involved. This provision has been the cause of some confusion on the part of the research community. According to the language of 45 CFR 46, research on specimens that are linked, even through a code, to personal information about the tissue source constitutes research on a human subject and is subject to the federal regulations.

For example, imagine a researcher interested in doing 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 samples 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 never recorded at the time the samples were collected. Thus, even if the investigator and the repository were to attempt to recontact the tissue donors, it would be impossible, because their identities are entirely unknown and unknowable. In this scenario, according to the regulations, there would be no human subject of research involved; no IRB review would be necessary, nor would consent from the tissue donors for new and unanticipated forms of research be required.

A different situation develops when tissues are identified in the human biological materials collection but the identifiers are stripped before release to an investigator. Imagine, for example, that an institution called HBM Collection of America ("CoA") has a number of tissues from kindreds. Investigator Smith requests samples from a family with achondroplasia (dwarfism). CoA takes samples from Family Jones, strips all references to the family name "Jones," and supplies them to the investigator marked only by position within the family group, for example, "father," "mother," "maternal aunt," or "son." The investigator has no way of knowing that the samples come from the Family Jones, and thinks of the samples as truly unidentifiable. If CoA has not kept 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

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

informed consent is required. However, if CoA has kept a record that it sent "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 CoA knows (name of family). The federal regulations are ambiguous as to whether this meets the definition of "identifiable," although it would appear that it could. Keeping in mind that one of the reasons for being concerned with identifiability of the family is to assess the possibility that research information could flow back to the tissue source, this scenario appears to describe a situation in which information could be linked between the investigator and a particular member of family (with some added difficulty if there is more than one maternal aunt or son).

Even more complex than the scenario just described is if CoA 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 part of the small group that makes up these three families. If the investigator were to provisionally discover that samples from one of the families provided by CoA indicated that its sources were at some risk of significant illness, there could certainly be a temptation to send this ambiguous but possibly useful information back to the sources via CoA's record of which family's samples were under investigation.

Finally, under the federal regulations, only living individuals can 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 or not prior informed consent was obtained. Such research may, however, be subject to the requirements of applicable State law. Of course, there may be ethical concerns regarding the use of such tissues beyond the scope of current law or regulation. In addition, where research using samples from deceased individuals involves identifiable private information about their living relatives, those relatives may themselves be ?human subjects" under the HHS regulations and must be afforded all required protections. Indeed, certain types of genetic research or research on families could pose risks for living relatives of the deceased. For example, if research was conducted on autopsy material of an 30-year-old woman who died in a traffic accident, and it was inadvertently found 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 move into a high-risk category for Huntington's Disease. Were they to be informed of this finding they would then face the prospects of being tested, coping with the psychosocial aspects of being at risk, and face possible future health insurance and possibly employment discrimination.

4. For research requiring review, what are the IRB requirements?

For situations in which individuals who provide biological material are identifiable and, therefore, the federal regulations apply, two basic protections for human subjects generally come into play. First, IRB review is required to ensure an acceptable balance between risks and

benefits, and second, subject enrollment is permitted on the condition that informed consent is properly obtained. There are, however, exceptions and variations that are pertinent to research on human biological materials.

First, the twin protections of consent and IRB review do not apply if the research is found to be exempt from the federal regulations. The person given the authority to determine if an exemption applies will vary among institutions, depending upon the assurance they negotiated with the government. In many cases, that person 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 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)).

Currently, OPRR interprets this regulation to mean that investigators who conduct research with coded samples are not eligible for the exemption if there is any means by which the codes could be broken (including by cooperation with other people and institutions) and specific research results linked to specific subjects.

INFORMED CONSENT REQUIREMENTS

All human subjects research generally requires consent but this requirement can be altered or waived if certain criteria, set forth at 45 C.F.R. Sec. 46.116(d), are met:

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 be practicably carried out without the waiver or alteration; and
4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

The meaning of "minimal risk," therefore, is central to determining if a protocol is eligible for a waiver of the consent requirements. It is also a key consideration in determining whether a protocol is eligible for expedited review.

EXPEDITED IRB REVIEW

For research that is not exempt from IRB review and informed consent by the subject, there are nonetheless opportunities for streamlining the review process in some cases and obviating the need for consent.

First, an IRB may use expedited review procedures when a protocol involves no more than minimal risk [46.110]. In short, the IRB chair or one or more experienced reviewers, designated by the chair from among members of the IRB, review the research and approve it or refer it to the IRB for full IRB discussion. To qualify for expedited review, an activity must: (1) involve no more than minimal risk and be found on the list published at Federal Register 46: 8392; Jan. 26, 1981;[6] or (2) be a minor change in previously approved research during the period of one year or less for which approval is authorized by the IRB.

[6] This list, which is currently being revised, includes: 1) collection of hair and nail clippings, in a nondisfiguring manner; deciduous teeth; and permanent teeth; if patient care indicates a need for extraction; 2) collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor; 3) recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practices; 4) collection of blood samples by venipuncture, in amounts not exceeding 450 ml in an 8-week period and no more often than 2 times per week, from subjects 18 years of age or older and who are in good health and not pregnant; 5) collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted techniques; 6) voice recordings made for research purposes; 7) moderate exercise by healthy volunteers; 8) the study of existing data, documents, records, pathological specimens, or diagnostic specimens; 9) research on individual or group behavior or characteristics of individuals; 10) research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required (46 FR 8392; January 26, 1981).

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 the subject. This assessment will depend upon the kind of information being sought in the specimen, the psychosocial and clinical significance for the subject, and the likelihood that the finding will be transmitted to the subject, or to anyone else who could associate the findings with the subject.

IRB CONCERN FOR THIRD-PARTY INTERESTS

The federal regulations are focused on living individuals. They ask if an individual is "identifiable." If they are, this individual is almost always entitled to be asked whether they wish to be a human subject of research. The IRB is asked to review the protocol to assess its risks and benefits to each individual subject. Nowhere in this process are the concerns of third parties explicitly taken into account.

And yet, research on one individual may reveal important, even dangerous information about others. Genetic testing on corpses, as noted above, can yield information on living relatives. And testing on a number of disparate individuals may yield information pertinent to many unrelated people who share salient characteristics, such as race, ethnicity, or possibly even 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.

The strict focus that the regulations place on the interests of the individual research subject, in the view of some, can be problematic in the context of research with human biological materials, and they believe that some attention should be paid to considering ways in whicb third party interests can be considered and be protected where appropriate.

APPLYING THE REGULATIONS TO A TYPICAL PROTOCOL: ISSUES FOR IRBS

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

Under current regulations, any link between the specimens used by the researcher and the men from whom the materials were obtained would make the activity "human subjects research." This identifiability, even if mediated by coding systems, would trigger the requirement for IRB review. The review might be eligible for expedited procedures, however, if it were deemed to be of minimal risk to the subjects and fulfilled the other requirements for expedited review.

If the initial screen of all samples, done solely for the purpose of identifying which men have the gene was done with unlinked samples, according to the regulations, the research would be exempt from IRB review. However, this would only allow for the researcher to receive a one-time, limited amount of clinical and demographic information at the time that the sample was sent from the repository. If the researcher chose to use coded samples, so as to be able to obtain the follow-up information or to communicate information back to the source of the sample, the research might qualify as minimal risk. This would depend on the likelihood that any finding would be communicated to the individual tissue donors and whether such communications pose the risk of significant psychosocial distress.

If the research was performed using coded samples, this would allow for a second screen in which the subset of men whose tissues show a marker for the gene will have their medical records examined. The same issues about minimal risk apply to this screen, but with a seemingly greater risk that findings will develop in the course of research that might prompt investigators to consider communicating their finding to the tissue donors or their physicians. For example, if the data strongly indicate that those with the markers respond dramatically better to one treatment than another, investigators may wonder whether it would be best to communicate this information to patients and their physicians so that the better treatment can be pursued before the patient's health irreversibly declines.

At the same time, the tentative nature of these findings, in the view of many, may make their communication problematic. Since some prostate treatments may have significant side-effects, such as impotence and incontinence, and since the clinical data on the need to detect and treat slow-growing prostate cancers in older men is mixed, such tentative findings may put patients into a position of 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 expedited review so difficult.

Psychological risk includes the risk of harm from learning genetic information about oneself (e.g., that one is affected by a genetic disorder that has not yet manifested itself). Complicating the issue of communicating genetic information to a subject is that typically the information is limited to probabilities. Furthermore, genetic data carries with it a margin of error; and some information communicated to subjects will, in the end, prove to be wrong. In either event, participants are subjected to the stress of receiving such information. For example, researchers involved in developing presymptomatic tests for Huntington Disease have been concerned that the emotional impact of learning the results may lead some subjects to attempt suicide. They have therefore asked whether prospective participants should be screened for emotional stability prior to acceptance into a research protocol.

Note that these disclosures of information can also be beneficial to the subject. One of the primary benefits of participation in genetic research is that the receipt of genetic information, however imperfect, can reduce uncertainty about whether participants will likely develop a disease that runs in their family (and possibly whether they have passed the gene along to their children). Where subjects learn that they will likely develop or pass along the disease, they might plan differently for the future. To minimize the psychological harms presented by pedigree research, it would be prudent for IRBs to make sure that investigators will provide for adequate counseling to subjects on the meaning of any genetic information they might receive. Genetic counseling is not a simple matter and must be done by persons qualified and experienced in communicating the meaning of genetic information to persons participating in genetic research or persons who seek genetic testing.

Regardless of whether expedited review is permitted by the local IRB or standard review is required, the IRB may then consider whether subject consent to do the research can be waived. Once again, the question of minimal risk must be answered. In addition, the investigators would need to show that doing the research without subject consent is necessary because it is impractical to contact the donors, and that doing the research without consent will not affect the rights of the subjects.

Given the subtlety of these inquiries, it would not be surprising to find that there is a great

deal of variation in the way IRBs deal with these issues. Some, for example, might find that the initial screening to identify the subset of samples with markers for the gene ought to be eligible for expedited review and a waiver of consent, but that subsequent work on the subset ought to require full review and subject consent. Others might waive consent for all aspects of the research, and still others for none.7

This variability in IRB response is relevant, because many protocols will involve repositories at one institution, and investigators at one or more different institutions. Since the regulations require that each institution's own IRB conduct its own review, the repository and the investigators may find that they are being held to different rules about the need to obtain consent. This phenomenon, a common occurrence in collaborative research of all types, has drawn criticism from the research community, as it adds to the time and complexity of getting all necessary approvals. For example, a researcher at Institution A, which has decided that consent is required for all stages of the work, might be precluded from collaborating with an investigator from Institution B, where consent requirements were waived. The decision about whether to permit the collaboration will lie in the hands of Institution A's IRB.

The justification for multiple IRB reviews lies in part in the philosophy of local review to reflect local standards of human subjects protections, and in part on the expectation that IRBs are

7 For example, NBAC heard testimony from Dr. Christopher Hook, Mayo Clinic, regarding his institution's practice of considering all human genetic studies as more than minimal risk, thereby warranting special review, testimony, May 20, 1998.

fallible, and that multiple reviews minimizes the possibility of a serious error due to the incorrect ruling by one particular IRB.

PROFESSIONAL STANDARDS

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. A number of these organizations developed position statements and recommendations that reflected their efforts to work through the many ethical and policy issues the topic raises. To provide NBAC with an understanding of the range of positions that exist among organizations which have carefully considered this subject, 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.[8]

Definitions: What Does "Identifiable" Mean?

As discussed earlier in this chapter, current human subjects regulations only distinguish between information that does or does not allow identification of an individual. But as professional groups consider what constitutes information sufficient to identify an individual,

[8] Fourteen statements, published and widely discussed in the literature, or available on the World Wide Web, were reviewed. For the results of this analysis, see Table_ in the Appendix.

some have constructed a number of categories that define degrees of biological material identifiability. Consequently, when groups discuss "identifiable" samples they may mean different things.

Although groups used different terminology to describe materials, four categories describing levels of identifiability of human biological materials were discussed in the reviewed statements. For the purpose of the comparative analysis, the terms describing categories of human biological materials were adapted from two of the sources to yield the following:[9] Anonymous biological materials were originally collected without identifiers or are otherwise impossible to link to their sources; Identifiable biological materials are either directly identified or coded, such that a subject can be identified either directly or through decoding; such materials are not now or are not expected to be made anonymous; Coded biological materials are unidentified for research purposes, but can be linked to their sources through the use of a code; Directly identified biological materials are those to which identifiers, such as a name, patient number, or clear pedigree location, are attached and made available to researchers.

When to Require Informed Consent and IRB Review

[9] These definitions are adapted from those discussed by the American Society of Human Genetics, Statement on Informed Consent for Genetic Research, 1996; and Clayton, E.W., Steinberg, K.K., Khoury, M.J., Thomson, E., Andrews, L., Kahn, M.J.E., Kopelman, L.M., and J.O. Weiss, Informed Consent for Genetic Research on Stored Tissue Samples, *JAMA* 274:1786-

Many groups recommend different protections according to the degree to which samples used in a research protocol can be identified with a subject. Therefore, how a group defines what constitutes identifiable information is important when considering what protections it recommends. Primarily to gain an understanding of what the various organizations discussed in terms of the appropriate level of protection, NBAC examined what protections the statements recommended for permissible use of existing, and permissible future collection and use of human biological materials. This comparison helped the Commission understand the range of protections and some innovative ideas for protections that have been discussed by some of these organizations.

The statements varied in precision and comprehensiveness: Not all of the statements explicitly distinguish between categories of sample identifiability; those that do distinguish do not necessarily address the issue of protections according to each category; and some do not explicitly address protections for permissible use of existing materials, but instead provide guidelines for collecting materials in the future. Overall, there was more discussion regarding protections for future collection than for the use of existing materials.

Two protections that appear throughout most of the statements, although they are not applied uniformly, are informed consent and institutional review board (IRB) review. Some statements provide guiding principles or factors to consider when making decisions about the

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appropriate use of materials in research. Others explicitly recommend the application of these protections to categories that indicate how readily identifiable the sample is.

The varied terminology used when professional groups discuss the identifiability of materials has not contributed to a standardization of practices. Lori Andrews and Dorothy Nelkin demonstrate an example of the difficulties that arise when terms are not defined or applied uniformly in the course of a comparison in a recent article (Andrews, 1998).

The American Society of Human Genetics (ASHG) does not use the classification "anonymous use" in its recommendations (ASHG, 1996). It does, however, discuss the appropriate use of anonymous or anonymized materials stating, "[obtaining consent] should be encouraged, except for the prospective studies in which samples are collected anonymously, or have been 'anonymized.'" This position seems to contrast with the position Andrews and Nelkin describe. However, if Andrews and Nelkin are using the phrase "anonymous use" to apply to "identifiable" samples (a term that is used in the ASHG statement) that are coded and could be said to be used in an anonymous manner in the research, then their interpretation of the statement would be accurate. Nonetheless, there is no textual or contextual evidence in the ASHG statement to support the imposition of a system of classification based on how the tissues are *used* in research. In other words, there is no justification for applying the category "anonymous use" to "identifiable" samples.

In that organizations have reached different conclusions regarding the meaning of "identifiable" samples, an obvious source of variation in recommending protections is different understandings of whether coded samples should be considered identifiable. Where some statements discuss "identifiable" samples they mean exclusively "coded" materials; others use "identifiable" to encompass both "coded" and "directly identified" materials. Statements developed by ASHG and the National Institutes of Health/Centers for Disease Control and Prevention (NIH/CDC) Workshop (Clayton, 1995) illustrate these two uses of "identifiable."

ASHG provides a table indicating "[s]uggested guidelines on the need to obtain informed consent in genetic research, by type of study design and level of anonymity." (ASHG, 1996)??In this format, the statement indicates explicitly whether informed consent should be required for each "level of anonymity" of the sample. Although ASHG differentiates between "identifiable" (meaning coded) and "identified" (meaning directly identified) samples, it recommends the same protections for both.

The NIH/CDC Workshop does not differentiate between coded or directly identified samples when applying protections. According to the Workshop participants, Even if the researcher cannot identify the source of tissue, the samples are not anonymous if some other individual or institution has this ability" (Clayton, 1995). Accordingly, they propose, "All research that proposes to use samples that are not now or will not be made anonymous requires

more thorough review." Thus, with regard to IRB review and informed consent, coded and directly identified materials deserve equal levels of protection.

The Pathologists Consensus Statement recommends, with regard to identifiable samples, that different protections be applied to research using archived, coded samples than to research using 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" (Pathologists, 1997). In this way, they reason, the research use of coded materials does not pose the same risks to subjects as the use of directly identified materials, and does not require the same protections. Instead, the statement proposes the following:

> When information about the specimen source is withheld from researchers and any link is provided only through IRB-approved confidentiality procedures, the risk to research subjects from unauthorized breach of confidentiality is minimal. We therefore recommend that where institutions and IRBs approve confidentiality policies and regard them as providing sufficient protections for patients from improper disclosure of information in the medical record, such approval should be regarded as adequate evidence of the ability to secure medical record information for research applications.

Decisions about the Appropriate Use of Existing Samples

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 the following: (1) when and how to recontact individuals regarding consent for new research uses of their samples; (2) how to judge the adequacy of previously given consent; and (3) how to assess protocols that propose to remove identifying information from samples before using them in research.

The statement from the American College of Medical Genetics (ACMG, 1995) 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."

A statement developed by the National Heart, Lung, and Blood Institute (NHLBI, 1997) lists several issues for IRBs and funding agencies to consider "[i]n judging the adequacy of a previous informed consent when an application is received to do new genetic research": "(1) the nature of the disease proposed for study, (2) the likelihood that knowing results of the research will harm or benefit an individual, (3) the availability of effective treatment or prevention for the

disorder, and (4) the burden of such treatment."

When it is determined that it would be inappropriate to use samples without contacting individuals, the ACMG also provides guidance regarding how to recontact individuals: "Contacts regarding new research should address its purpose, limitations and possible outcomes, methods for communicating and maintaining confidentiality of results, duration of storage, uses of samples or results in studying others (anonymously), and sharing samples with other researchers for other types of research" (ACMG, 1995).

Another complex decision IRBs must address when research with stored samples is proposed involves judging the appropriateness of removing identifiers from samples. The NIH/CDC Workshop statement lists five factors for IRBs to consider "in deciding how to assess protocols that propose to make existing identifiable samples anonymous for use in research": (1) whether the information the researcher seeks can be obtained in a manner that allows individuals to consent (this includes the possibility of using tissue samples for which people had previously given permission for use in research); (2) whether the proposed investigation is scientifically sound and fulfills important needs; (3) how difficult it would be to recontact subjects (it is not necessary, however, to prove impracticability); (4) whether the samples are finite and, if used for research, they may no longer be available for the clinical care of the source or his or her family (for example, use of tumor samples may be more problematic than

use of transformed permanent cell lines); and (5) how the availability of effective medical interventions affects the appropriateness of pursuing anonymous research (Clayton, 1995).

Collecting Samples with Appropriate Informed Consent

When collecting human biological materials from individuals in a research or clinical setting, an informed consent process that allows individuals choices regarding how the sample will be used after the original protocol or procedure, is an important element in the protection of individuals' interests and facilitation of research. Many 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 is comprehensible to patients and research subjects. The types of consent proposed ranged from general consent (consent to future, unspecified research uses of the material), to layered consent (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 discussion regarding what level of consent is appropriate for the use of materials. Regarding general consent, ASHG 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." On the other hand, the Pathologists Consensus Statement notes that there may be value in requiring general consent stating, "[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" (Pathologists, 1997).

Several statements advocate a form of layered consent for collecting all samples in the future. NHLBI provides thoughtful discussion on the content of a proposed three-tiered consent. In such a consent, as NHLBI describes, one 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).

Highlighting the importance of designing adequate informed consent mechanisms in the future, the National Action Plan on Breast Cancer National Biological Resource Banks Working Group [10] focuses primarily on future collection and use: "The Working Group believes that when organizations with access to specimens act according to the following criteria, it should generally be unnecessary to obtain further consent from patients." The group acknowledges that its principles apply to "prospective specimen collection," and does not make explicit

[10] *Model Consent Forms and Related Information on Tissue Banking from Routine Biopsies*, Compiled by the National Action Plan on Breast Cancer Tissue Banking Working Group, with comments by the PRIM&R/ARENA Tissue Banking Working Group, 1997.

recommendations for the use of existing samples. However, these carefully developed principles can be adapted "to allow . . . pathologists to make their collections available for research and, at the same time, protect the privacy and confidentiality of the tissue sources."

In addition to principles for IRBs to consider, the NAPBC has developed a model consent document and information sheet that provides answers to questions likely to arise from patients and their families. An NAPBC working group developed the model consent form using "information and ideas from existing IRB-approved forms, discussions with representatives of the breast cancer clinical and research communities, and 27 focus groups" drawing from diverse groups outside of the health care community. The consent form develops the layered consent approach in that the subject is offered the opportunity to consent to a certain class of or all future research. While these materials grew out of efforts to address concerns of the breast cancer community, they address many of the issues arising from the use of human biological materials in general.

Additional Protections

In addition to IRB review and informed consent, some organizations have discussed ideas for other protections. NHLBI has outlined a proposal for an advisory board to manage the use of stored materials:

NHLBI should establish a facilitator function for the valuable resource of stored specimens. Similar to other valuable collections, the facilitator will maintain organization and control access to utilization. The facilitator function should be carried out by an Advisory Board, including some of the original investigators who collected the specimens, genetic researchers similar to those who will request specimens, and the public. Specifically, this NHLBI Advisory Board must attend to informed consent issues, carefully reading previous consent documents and considering their applicability to current requests, based on the guidelines set forth above. To enhance public accountability, the Advisory Board and investigator(s) should seek advice about consent issues from members of the group whose tissues will be studied (NHLBI, 1997).

IRB-approved policies for protecting confidentiality contribute an additional layer of protection in the research process. Groups such as those endorsing the Pathologists Consensus Statement have expressed the view that these policies are an important element in any policy governing the research use of human biological materials that seeks to protect human subjects. They reason that where these mechanisms are in place, IRBs should be permitted "broader latitude to waive the requirements for informed consent for research on identifiable (linkable or coded) samples" (Pathologists, 1997).

The effectiveness of institutional confidentiality policies is central to any system where

masking individuals' identities by coding samples is used as a way of protecting privacy and maintaining confidentiality. The Association of American Medical Colleges (AAMC) describes the importance of maintaining access to patient information through the use of coding mechanisms:

> A great deal of contemporary research is dependent on the ready accessibility of personally identifiable, i.e., linkable, archival patient materials, such as medical records and tissue specimens removed in the course of routine medical care . . .. As a rule, these kinds of studies [epidemiologic and health services research] do not require that the identity of the patient be known to the investigator. But in the great majority, the investigators must have the ability to obtain additional, or follow up information about particular sets of subjects in order to evaluate the significance of the findings and interpret them in an appropriate biological, clinical or epidemiological context. The only way such additional information can be gathered in studies of archival patient materials is if the materials are coded in such a way that they remain permanently linkable to specific patients (AAMC, 1997).

The AAMC also proposes one way that secured access to such information could be maintained:

> One possible approach to this task would be to give each patient at his/her first encounter with the health care system two unique identifiers, one for clinical use, the other for

research. Both numbers would be permanently associated with the specific individual. The linkage between the two numbers would be securely maintained in a protected location with controlled access . . . . (AAMC, 1997).

In sum, professional groups varied in the way they defined the categories of anonymity of samples and the protections recommended for each category. Several have developed guidelines for IRBs and investigators as they confront the questions that arise when research is proposed using existing materials. Finally, these statements contained some but not explicit discussion about the mechanisms for ensuring the materials are stored and/or used in such a way that the confidentiality of the source of the material is promoted.

INTERNATIONAL PERSPECTIVES ON THE USE OF HUMAN BIOLOGICAL MATERIALS IN RESEARCH

At the international, regional, and national levels the use of human biological materials has been the focus of much current attention. Governmental, non-governmental and professional bodies at various levels have cited the increasing value of human biological materials, the need to ensure that they are used in an ethical manner, and the lack of clear policy as factors making the issuance of guidelines timely.

Statements addressing the ethical use of human tissues in research were issued this year

(1998) by the European Group of Ethics (EGE) advising the European Commission, Human Genome Organisation (HUGO), Tri-Council of Canada, and World Health Organization (WHO). An overview of these recently issued statements provides a sense of how groups outside the United States are currently addressing these issues11.

The EGE, an advisory committee to the European Commission, issued an ***Opinion on Human Tissue*** *Banking* (1998) that covers a wide variety of human tissues used for diagnostic, therapeutic, and research purposes. Noting a lack of legislation specifically addressing the use of human tissue, the Opinion attempts to address the "urgent need to regulate the conditions under which human tissues circulate within the European Market."12

In contrast to statements NBAC reviewed issued in the United States that deal with stored tissue, the Opinion focuses primarily on regulating therapeutic uses of tissue (e.g transplants), noted as the most common use of human tissue. In accordance with this focus, the EGE stresses safety as an ethical imperative and calls for strict controls of human tissue banks. It recommends a system that would protect the identity of the source ("confidentiality") while permitting that the source be traced if necessary to address matters of safety of the donated tissue ("traceability"). As stated, "The Group moreover calls for strict controls of the human tissue banks' activities

11 For a more in depth analysis of ethical and legal policy statements on the use of DNA samples in human genetic research from governmental, non-governmental and professional bodies at the international, regional and national levels, see Bartha M. Knoppers, et al "Control of DNA Samples and Information" (A report commissioned by the National Bioethics Advisory Commission), September 17, 1997.

12 In its definition of tissue, it does not include solid organs or blood which are already covered by national legislation in

which should be subject to an authorization. The banks need, in particular, to ensure the traceability of tissues which allows for, in the event of subsequent adverse effects, tracing the donor's identity and medical file."

The EGE calls for respecting "fundamental ethical principle, common to the European countries:

- *Donation of human tissue must be free . . .*
- *Anonymity of the donation . . .*
- *Requirement of prior consent on the basis of national legislative rules (explicit or presumed consent, before a witness, registration of agreement to donation, or on the contrary, refusal of donation). Information prior to the consent has to be provided to the donor, even in case of surgical residues.*
- *The respect for private life and medical confidentiality concerning the donors and their families (collected data may also refer to ancestors)."*

The EGE notes that it took into consideration the work of community, European, and international legislation in the development of the document and, in particular, the above ethical principles. It cites the Council of Europe's *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine* (April 1997) and UNESCO's *Declaration on the Human Genome and Human Rights* (November 1997)

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all Member States of the European Union.

as two influential documents. Both incorporate, as does the EGE's Opinion, ethical principles such as consent, respect for privacy, the right to information, non-discrimination and the prohibition of financial gain from the human body.

The EGE Opinion 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. It notes that "It is difficult to identify which institution collects and stores tissues in the Member States of the European Union and only few specific pieces of legislation exist." In many countries legislation has not caught up with the "considerable increase in tissue uses for medical research," and currently deals mainly with organ transplantation.

The HUGO Ethics Committee issued a ***Statement on DNA Sampling: Control and Access*** (1998) that addresses several ethical issues pertinent to sample collection and sharing in genetic research. It states as a matter of primary importance the source of the sample, "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."

It 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 HUGO Ethics 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). Such samples may be used if, provided there is ethical review, they have been anonymized prior to use. All other samples (i.e. samples collected in clinical care or research where there is general notification) may be used if, again provided there is ethical review, the patient or participant "has not yet objected, and the sample to be used by the researcher has been coded or anonymized."

Addressing research conducted in the future, the HUGO Ethics Committee provides recommendations as to what choices should be offered in the consent process. It lists as important information to include in the process the potential uses of the sample and its information. The consent process should also 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 remarkable for its focus on protecting the rights of family members in addition to those of the individual source. 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 "where 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.

The Tri-Council of Canada13 this year issued the ***Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*** that describes standards and procedures for governing research involving human subjects. In a section devoted to the use of human tissue in research the Tri-Council addresses issues of privacy and confidentiality, free and informed consent, and the use of previously collected tissue. Elsewhere in the comprehensive document, other concerns raised by human genetic research such as protecting families and biological relatives and the banking of genetic material are discussed.

The Tri-Council distinguishes four categories of tissue: Identifiable (can be immediately linked 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 Tri-Council notes that even where 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

13 The Tri-Council of Canada is composed of the Medical Research Council of Canada, the Natural Sciences and

tissue." It states as a requirement that researchers involving families and groups in genetic research reveal potential harms to the ethics board and outline how the harms will be dealt with.

The Tri-Council also addresses how to obtain consent when collecting new material for research. It recommends that potential donors of tissue be informed about, among other things, "the type and amount of tissue to be taken, as well as where the tissue is to be taken; the potential uses for the tissue including any commercial uses; the safeguards to protect the individual's privacy and confidentiality; and identifying information attached to specific tissue, and its potential traceability."

Finally, the WHO Human Genetics Programme in 1998 issued ***Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services*** that devote a section to "Banked DNA." 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 re-contact that may be established in the future." 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 re-contact before each new research project."

Addressing samples to be collected in the future, it recommends a list of issues to consider when policies are developed: 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 among collaborators; Advantages and disadvantages for individuals and researchers of removing all identifiers from a sample.

The WHO's Guidelines, like those issued by HUGO, discuss the interests that biological relatives have in the control of DNA specimens. It 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."

In sum, NBAC's review of these statements revealed 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 non-commercialization of the body. There seems to be a common position emerging to the effect that a person's rights and interests are best protected if that person has some form of control over his or her removed

genetic material. It is clear that at the international and regional level, informed consent with regard to DNA sampling in genetic research is still expanding to include more information and choices beyond the "yes"/"no" of participation in medical research in general. Nonetheless, there exists a rich diversity of positions on how to control access to and use of human biological materials and the data obtained from them. Basic standardization of policies with regard to the use of DNA samples in research can facilitate international cooperation.

OTHER CONSIDERATIONS: MEDICAL RECORD PROTECTION AND HUMAN SUBJECTS RESEARCH

Many protocols calling for research use of human biological materials will also require information from relevant medical records to accompany the tissue. Such information would allow investigators to correlate characteristics of the tissue with characteristics of the etiology and course of the patient's disease and the patient's response to various treatments. For this reason, it is not enough for NBAC to study the rules currently governing access to human tissue for research; it must also look at rules governing access to medical records. Where NBAC contemplates changes in the current regime governing tissue research, it will be important to ensure that the changes are compatible with rules governing medical records.

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 for research on the patient/subject. Indeed, the regulations governing tissue use and medical record use are basically the same and on a practical level treat tissue as simply another form of a medical record.

Currently, no federal law protects the privacy of medical records, unless the records are actually held by the government. Recent legislative movements, however, have sought to address this deficiency. 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 to make recommendations to Congress, in consultation with the National Committee on vital and Health Statistics (NCVHS), 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.14 On August 11, 1998, HHS 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

14 National Health Policy Forum Issue Brief No. 724, p.2.

technical guidance require all parties who deal with electronic health information to establish responsible and appropriate safeguards, develop a security plan, provide training for employees, secure physical access to records and implement a digital signature regimen to verify the identity of the person accessing medical records.15

Although the 105th Congress considered several attempts to craft medical privacy legislation, no law was passed during the 1998 session. The major patient protection bills under consideration all contained confidentiality provisions and gave individuals the right to inspect and copy their medical records, except in special circumstances.16 In addition, several legislative proposals focused exclusively on medical records confidentiality.17 Such bills differed in their treatment of issues including the appropriate uses of personally identifiable information, whether federal regulations should be applied to both federally and nonfederally funded researchers that 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

15 American Political Network, Inc., Health Line, "Medical Privacy: HHS Introduces New Standards," August 12, 1998.
16 E.g., S. 2330, S. 1890/H.R. 3605, S. 2416, H.R. 4250.
17 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; "Patients' Bill of Rights Act of 1998," S. 2529.

approval by an IRB for federally funded and nonfederally funded research.[18] One particular bill permitted disclosure to health researchers if the disclosure was "reviewed by a committee, board, or informal organization in accordance with confidentiality standards specifying permissible and impermissible uses of the information."[19] Another permitted a health researcher to obtain protected health information only under the following circumstances:

> (1) from federally funded projects or institutions that have assurances on file with the Office of Protection of Human Subjects at the National Institutes of Health in compliance with rules specified by the federal government; (2) in conformance with rules promulgated by the Food and Drug Administration for new product trials; or (3) if the research is privately funded human subject research.

The bill acknowledged that there are currently no specific procedures in place for the third classification of research. It provided for the Senate Committee on Labor and Human Resources to await the recommendations of the secretary of health and human services, after reviewing the commissioned General Accounting Office study on confidentiality and NBAC's report, to determine appropriate confidentiality procedures for privately funded human subject research. [20]

Finally, the legislative initiatives generally differed on whether to establish a floor or a ceiling for federal standards. Many would have preempted most state laws except those pertaining to mental health and public health activities.[21] Others would not have preempted any state laws that provide a greater level of protection for personally identifiable health

18 See S. 1368, H.R. 52, H.R. 1815.
19 H.R. 3900.
20 S. 1921.
21 See S. 1921, H.R. 52, H.R. 3900.

information.22 The latter position is generally consistent with the recommendations presented to Congress by DHHS.

General statutory and common law rules lay the groundwork in many states for a claim of privacy as 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.23 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.24 In most instances, these acts are aimed at preventing the use of such personal medical information by insurance companies and employers, and thereby protecting the individual from discrimination and/or stigmatization. The variability of state law protections has been cited as a problem in itself, regardless of the privacy protections offered by the states. 25

Where statutes exist, they may specifically contemplate access to medical records for research use. California's medical records confidentiality law, for example, states that the "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

22 S. 1368, H.R. 1815.

23 See William H. Minor, "Identity Cards and Databases in Health Care: The Need for Federal Privacy Protections," 28 Colum. J.L. & Soc. Probs. 253 (Winter 1995); Robert E. Smith, Compilation of State and Federal Privacy Laws (1992).

24 See Compilation of Privacy Laws; Office of Technology Assessment, U.S. Congress, Protecting Privacy in Computerized Medical Information (1993); Sheri Alpert, "Smart Cards, Smarter Policy: Medical Records, Privacy, and Health Care Reform," 23 Hastings Center Rep., Nov.-Dec. 1993.

25 Marianne Lavelle, Health Plan Debate Turning to Privacy, Nat'l L.J., May 30, 1994, at A1.

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."26 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,"27 language which is very 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."28

Florida and Minnesota laws also specifically address 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

26 Cal. Civ. Code Ann. § 56.10 (c)(7) (West 1982 & Supp. 1998).
27 Id. § 56.05(b).
28 Id. § 56.17.

providers involved in the care or treatment of the patient, except upon written authorization of the patient."29 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."30

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.31

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:

> (i) 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
>
> (ii) use reasonable efforts to obtain the patient's written general authorization that describes the release of records in item (i), which

29 Fla. Stat. § 455.667(5) (1997).
30 Id. § 455.667(5)(d).
31 Minn. Stat. § 144.335 subdivision 3a (1997).

does not expire but may be revoked or limited in writing at any time by the patient or the patient's authorized representative.

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

(i) the use or disclosure does not violate any limitations under which the record was collected;
(ii) 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;
(iii) 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
(iv) 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.32 Many of these initiatives attempt to protect an individual's privacy interest by preventing the dissemination of personal information—doing 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

32 See, e.g., 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;

records can be disclosed only if one of two conditions is fulfilled: either the patient gives 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 is oftentimes not defined by the legislative initiatives and also varies from state to state. Several 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 source of the sample with greater control over its uses by giving the source a legal property right in the sample and information that is derived therefrom.33 To date 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.34

What appears clear from the state legislative initiatives is that there is a perceived need to protect medical information from possible negative consequences of research conducted on human biological materials. This need is particularly pronounced where the information may

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1997 DE S.B. 153.

33 See e.g., 1998 UT H.B. 271; 1997 MI H.B. 5459.

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

identify the individual.

Courts themselves have only recently begun to recognize individual "privacy" rights with respect to one's 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 from that era is quite strong in its condemnation of 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."35 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.36 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 particular case, the court held that "the public need prevailed over the claim that medical records in general were protected from discovery." Of course, it is not

35 93 Misc. 2d 201 (N.Y. Sup. Ct. 1977).
36 United States v. Westinghouse Electric Corp., 638 F.2d 570 (3d Cir. 1980).

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 in his HIV status because his personal medical condition is a matter that he is normally entitled to keep private.37 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 various types of privacy protection.38

CONCLUSIONS

In its deliberations, NBAC reviewed the applicability of the existing federal regulations pertaining to research with human biological materials. The Commission 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 on

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37 Doe v. City of New York, 15 F.3d 264, 267 (2d Circuit, 1994).

38 See, e.g., Alaska Const. art. I, section 22; Ariz. Const. art. II, section 8; Cal. Const. art. 1, section 1; Fla. Const. art. I, 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. See Comm. on Regional Health Data Networks, Inst. of Medicine, Health Data in the Information Age: Use, Disclosure, and Privacy at 147 (Molla S. Donaldson & Kathleen N. Lohr eds., 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. 2d 77 (Cal. Ct. App. 1991).

biological samples. Thus, there is resulting confusion about whether certain research is covered (based on how closely the samples are linked to their sources and how easily that linkage can be accomplished). The issue of identifiability is further confounded by the researcher's growing ability to identify the source (even when unidentified) because of the uniqueness of the clinical information that accompanies the material when it is delivered from the repository.

Second, the existing regulations are silent on the topic of group or community harm. Thus, protocols that pose insignificant risks to individuals but might implicate strong group interests do not get 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.

Third, the regulations offer insufficient guidance on the meaning of "minimal" psychosocial risk or the nature of the subjects' "rights and welfare" to be protected.

Fourth, the existing regulations do not make clear the status of living relatives of deceased individuals whose stored samples are used in research. Although OPRR has indicated that these people might 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.

Fifth, there are major unresolved issues pertaining to the on-going access to medical records that 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 might 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.

Finally, existing statements issued by numerous scientific and professional groups provided NBAC with a useful starting point for the development of its recommendations and highlighted the need for clarity in interpretation of the regulations.

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