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1 **Chapter 4**  
2 **Current Guidance on the Use of Human Biological Materials in**  
3 **Research**  
4

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

10

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

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1 **A BRIEF HISTORY OF HUMAN SUBJECTS PROTECTIONS**

2

3           The modern story of human subjects protections begins with the Nuremberg Code,  
4 developed for the Nuremberg Military Tribunal as standards by which to judge the human  
5 experimentation conducted by the Nazis.<sup>1</sup> The Code captures many of what are now taken to be  
6 the basic principles governing the ethical conduct of research involving human subjects. The first  
7 provision of the Code states that "the voluntary consent of the human subject is absolutely  
8 essential." Freely given consent to participation in research is thus the cornerstone of ethical  
9 experimentation involving human subjects. The Code goes on to provide the details implied by  
10 such a requirement: capacity to consent, freedom from coercion, and comprehension of the risks  
11 and benefits involved. Other provisions require the minimization of risk and harm, a favorable  
12 risk/benefit ratio, qualified investigators using appropriate research designs, and freedom for the

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<sup>1</sup> 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."

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1 subject to withdraw from that study at any time.<sup>2</sup> The Code makes no provision for waiver or  
2 omission of consent.

3

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

10

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

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<sup>2</sup> 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 35<sup>th</sup> World Medical Assembly, Venice, Italy; the 41st World Medical Assembly, Hong Kong, 1989; and the 48<sup>th</sup> General Assembly, Somerset West, Republic of South Africa, 1996. The Declaration of Helsinki further distinguishes therapeutic from nontherapeutic research.

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1           On September 30, 1978, the National Commission for the Protection of Human Subjects  
2 of Biomedical and Behavioral Research issued *The Belmont Report: Ethical Principles and*  
3 *Guidelines for the Protection of Human Subjects of Research*, which set forth the basic ethical  
4 principles underlying the acceptable conduct of research involving human subjects. Those  
5 principles—respect for persons, beneficence, and justice—are now accepted as the three  
6 quintessential requirements for the ethical conduct of research involving human subjects. The  
7 *Belmont Report* also describes how these principles apply to the conduct of research. Specifically,  
8 the principle of respect for persons underlies the need to obtain informed consent; the principle of  
9 beneficence underlies the need to engage in a risk/benefit analysis and to minimize risks; and the  
10 principle of justice requires that subjects be fairly selected.

11

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

18

19           These “basic” regulations became final January 16, 1981, and were revised effective  
20 March 4, 1983, and June 18, 1991. The June 18, 1991, revision involved the adoption of the  
21 Federal Policy for the Protection of Human Subjects. The Federal Policy (or “Common Rule” as it

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1 is sometimes called) was promulgated by 17 federal agencies that conduct, support, or otherwise  
2 regulate human subjects research; the FDA also adopted certain provisions of the Common Rule.  
3 As is implied by its title, the Federal Policy is designed to make uniform the human subjects  
4 protection system in all relevant federal departments and agencies. The Common Rule and other  
5 human subjects regulations are codified at Title 45 Part 46 of the Code of Federal Regulations,  
6 and it is the NIH Office for Protection from Research Risks (OPRR) that has taken the lead within  
7 the Federal Government on the task of harmonizing human subjects protections across agencies.<sup>3</sup>

8

9 **THE SCOPE OF THE CURRENT FEDERAL REGULATIONS**

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<sup>3</sup> 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.

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

3

4           **1. Is the research subject to federal regulation?**

5

6           The federal regulatory protections only apply to: 1) research supported by funding from  
7 one of the federal agencies subscribing to the Common Rule; 2) research on an investigational  
8 new drug, device or biologic subject to FDA rules; or 3) research conducted at an institution or  
9 by an individual investigator at that institution that has executed an assurance with the Federal  
10 Government stating that even research not otherwise covered by the regulations will nonetheless  
11 be governed by them.

12

13           For example, an investigator performing privately funded research at a large university  
14 that has executed a “multiple project assurance” with the Federal Government almost always will  
15 be required to abide by the federal regulations.<sup>4</sup> In addition, many multiple project assurance  
16 agreements include a provision that prevents researchers at that institution from evading federal  
17 regulation by conducting the research off-site or with a private, unregulated company. Instead,

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<sup>4</sup> 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 assurance of compliance to OPRR the document is called an Agreement.

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1 these multiple assurances typically promise that any researcher affiliated with the institution will  
2 abide by the federal regulations no matter where or with whom they work.

3

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

7

## 8 **2. Does the activity constitute research?**

9

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

15

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

20

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1           **3. Does the research involve a “human subject”?**

2  
3           “Human subject” is defined by the regulations as “a living individual about whom an  
4 investigator conducting research obtains: (a) data through intervention or interaction with the  
5 individual, or (b) identifiable private information” (46.102(f)(1)&(2)). Specifically,

6           Intervention includes both physical procedures by which data are gathered (for example,  
7 venipuncture) and manipulations of the subject or the subject’s environment that are  
8 performed for research purposes. Interaction includes communication or interpersonal  
9 contact between investigator and subject. Private information includes information about  
10 behavior that occurs in a context in which an individual can reasonably expect that no  
11 observation or recording is taking place, and information which has been provided for  
12 specific purposes by an individual and which the individual can reasonably expect will not  
13 be made public (for example, a medical record). Private information must be individually  
14 identifiable (i.e., the identity of the subject is or may readily be ascertained by the  
15 investigator or associated with the information) in order for obtaining the information to  
16 constitute research involving human subjects.  
17

18           From this definition it is apparent that an investigator who interacts with a person in order  
19 to obtain a new blood or saliva sample is doing human subjects research, regardless of whether  
20 the investigator records any personal information about the subject.

21  
22           When working with existing stores of biological materials, an investigator is defined as  
23 doing research on a “human subject” when he or she obtains “identifiable private information.”  
24 Section 46.102(f)(2) defines “i-identifiable” to mean “the identity of the subject is or may readily be  
25 ascertained by the investigator or.... associated with the information.” OPRR interprets  
26 “identifiable” to include specimens with codes that, with the cooperation of others, could be

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1 broken open in order to reveal the name of the tissue source.<sup>5</sup> On the other hand, according to  
2 the regulations, research on specimens provided to the investigator with no personal identifiers  
3 and where no codes linked to personal identifiers is maintained would not be covered by the  
4 regulations because no human subject would be involved. This provision has been the cause of  
5 some confusion on the part of the research community. According to the language of 45 CFR  
6 46, research on specimens that are linked, even through a code, to personal information about the  
7 tissue source constitutes research on a human subject and is subject to the federal regulations.

8

9         For example, imagine a researcher interested in doing basic work toward the development  
10 of the mapping and sequencing of the human genome. He or she might request tissue samples  
11 from a repository that has stored samples from an entire kindred. The samples are identified by  
12 position within the kindred (e.g., “father”, “daughter,” “maternal aunt”), but the identity of the  
13 family was never recorded at the time the samples were collected. Thus, even if the investigator  
14 and the repository were to attempt to recontact the tissue donors, it would be impossible, because  
15 their identities are entirely unknown and unknowable. In this scenario, according to the  
16 regulations, there would be no human subject of research involved; no IRB review would be  
17 necessary, nor would consent from the tissue donors for new and unanticipated forms of research  
18 be required.

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<sup>5</sup> Personal communication from Dr. Gary B. Ellis, Director, OPRR, April 8, 1998.

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1           A murkier situation develops when tissues are identified in the human biological materials  
2 collection but the identifiers are stripped before release to an investigator. Imagine, for example,  
3 that an institution called HBM Collection of America ("CoA") has a number of tissues from  
4 kindreds. Investigator Smith requests samples from a family with achondroplasia (dwarfism).  
5 CoA takes samples from Family Jones, strips all references to the family name "Jones," and  
6 supplies them to the investigator marked only by position within the family group, for example,  
7 "father," "mother," "maternal aunt," or "son." The investigator has no way of knowing that the  
8 samples come from the Family Jones, and thinks of the samples as truly unidentifiable. If CoA has  
9 not kept a record linking the samples to Family Jones, then, according to the regulations, no  
10 human subject is involved in the investigator's research on the samples, and no IRB review or  
11 informed consent is required. However, if CoA has kept a record that it sent "Family  
12 Jones"—and only Family Jones—to the investigator, then in fact the identity of each tissue source  
13 can be nearly or completely reconstructed by combining what the investigator knows (family  
14 position) with what CoA knows (name of family). The federal regulations are ambiguous as to  
15 whether this meets the definition of "identifiable," although it would appear that it could. Keeping  
16 in mind that one of the reasons for being concerned with identifiability of the family is to assess  
17 the possibility that research information could flow back to the tissue source, this scenario appears  
18 to describe a situation in which information could be linked between the investigator and a  
19 particular member of family (with some added difficulty if there is more than one maternal aunt or  
20 son).

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1           Even more complex than the scenario just described is if CoA provides samples from  
2 several family groups, e.g. Family Jones, Family Smith, and Family Williams. In this situation, no  
3 individual tissue source can be determined with precision, but each individual can be identified as  
4 part of the small group that makes up these three families. If the investigator were to  
5 provisionally discover that samples from one of the families provided by CoA indicated that its  
6 sources were at some risk of significant illness, there could certainly be a temptation to send this  
7 ambiguous but possibly useful information back to the sources via CoA's record of which family's  
8 samples were under investigation. It is unclear, again, whether the samples used in this manner  
9 would constitute "identifiable" samples under the regulation, thus triggering human subjects  
10 protections.

11

12           Finally, under the federal regulations, only living individuals can be human subjects.  
13 Research involving tissues from individuals who are deceased at the time of the research is not  
14 subject to the Common Rule, regardless of whether or not prior informed consent was obtained.  
15 Such research may, however, be subject to the requirements of applicable State law. Of course,  
16 there may be ethical concerns regarding the use of such tissues beyond the scope of current law or  
17 regulation. In addition, where research using samples from deceased individuals involves  
18 identifiable private information about their living relatives, those relatives may themselves be  
19 "human subjects" under the HHS regulations and must be afforded all required protections.  
20 Indeed, certain types of genetic research or research on families could pose risks for living  
21 relatives of the deceased. For example, if research was conducted on autopsy material of a 30-

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1 year-old woman who died in a traffic accident, and it was inadvertently found and disclosed that  
2 she possessed the gene for Huntington's Disease (which might not become manifest until age 50),  
3 then that woman's children automatically move into a high-risk category for Huntington's  
4 Disease. Were they to be informed of this finding they would then face the prospects of being  
5 tested, coping with the psychosocial aspects of being at risk, and face possible future health  
6 insurance and possibly employment discrimination.

7

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

9

10 For situations in which individuals who provide biological material are identifiable and,  
11 therefore, the federal regulations apply, two basic protections for human subjects generally come  
12 into play. First, IRB review is required to ensure an acceptable balance between risks and  
13 benefits, and second, subject enrollment is permitted on the condition that informed consent is  
14 properly obtained. There are, however, exceptions and variations that are pertinent to research on  
15 human biological materials.

16

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

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1 department in which the investigator works. In others, it will be the chair or the administrator of  
2 the IRB.

3

4 The regulations state that such an exemption may be applied to “research involving the  
5 collection or study of existing .specimens. . .if the information is recorded by the investigator in  
6 such a manner that subjects cannot be identified, directly or through identifiers linked to the  
7 subjects” (46.101(4)).

8

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

13

#### 14 **INFORMED CONSENT REQUIREMENTS**

15

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

18

- 19 1) the research involves no more than minimal risk to the subjects;  
20 2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;  
21 3) the research could not be practicably carried out without the waiver or alteration; and

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

3

4 The meaning of “minimal risk,” therefore, is central to determining if a protocol is eligible  
5 for a waiver of the consent requirements. One risk is that an investigator will discover something  
6 that tempts them to communicate the results to the tissue source. This might occur, for example,  
7 when preliminary results indicate the possible presence of a dangerous condition that might be  
8 ameliorated only with immediate medical attention.

9

10 Experts disagree about whether interim or inconclusive findings should be communicated  
11 to subjects. Many feel that they should not, because only confirmed, reliable findings constitute  
12 “information.” Persons who oppose revealing interim findings argue that the harms that could  
13 result from revealing preliminary data whose interpretation changes when more precise or reliable  
14 data become available are serious, including anxiety or irrational (and possibly harmful) medical  
15 interventions. They argue that such harms are avoidable by controlling the flow of information to  
16 subjects and limiting communications to those that constitute reliable information. MacKay  
17 (1984), writing about the development of genetic tests, argues against revealing interim findings,  
18 contending that preliminary results do not yet constitute “information” since “until an initial  
19 finding is confirmed, there is no reliable information” to communicate to subjects, and that  
20 “even...confirmed findings may have some unforeseen limitations” [p. 3]. He argues that subjects  
21 should not be given information about their individual test results until the findings have been

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1 confirmed through the “development of a reliable, accurate, safe and valid presymptomatic test”  
2 [pp. 2-3; see also Fost and Farrell (1990)]. Others have argued that the principle of autonomy  
3 dictates that subjects have a right to know what has been learned about them, and therefore, that  
4 interim results should be shared with subjects (Veatch).

5

6 Reilly (1980) suggests that IRBs develop general policies governing the disclosure of  
7 information to subjects to help make these determinations. He suggests that at least the following  
8 three factors be considered: “1) the magnitude of the threat posed to the subject; 2) the accuracy  
9 with which the data predict that the threat will be realized; and 3) the possibility that action can be  
10 taken to avoid or ameliorate the potential injury” [p. 5]. In this context he suggests that IRBs  
11 should ask investigators to define three categories of disclosure: 1) “findings that are of such  
12 potential importance to the subject that they must be disclosed immediately;” 2) “data that are of  
13 importance to subjects..., but about which [the investigator] should exercise judgment about the  
14 decision to disclose...[i]n effect, these are data that trigger a duty to consider the question of  
15 disclosure;” and 3) “data that do not require special disclosure” [pp. 5, 12].

16

#### 17 **EXPEDITED IRB REVIEW**

18

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

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

8

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

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<sup>6</sup> 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).

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## **IRB CONCERN FOR THIRD-PARTY INTERESTS**

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

9

10           And yet, research on one individual may reveal important, even dangerous information  
11 about others. Genetic testing on corpses, as noted above, can yield information on living  
12 relatives. And testing on a number of disparate individuals may yield information pertinent to  
13 many unrelated people who share salient characteristics, such as race, ethnicity, or possibly even  
14 the presence of a predisposing condition. This, in turn, could result in members of the group  
15 facing, among other things, stigmatization and discrimination in insurance and employment. What  
16 is at issue for both the individual research subject and the group is that the research might expose  
17 facts about them— namely, the higher probability of the occurrence of disease—which places  
18 them at risk of psychosocial harms.

19

20           Interestingly, there may even be circumstances where the individual research subject faces  
21 less risk of harm than other members of a group to which he or she belongs. For example, a  
22 socially and economically well-situated research subject will likely be a lower risk of suffering the

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1 effects of insurance and employment discrimination than less fortunate members of the group.  
2 Moreover, the stigma associated with a disease may be far more injurious to a group and its  
3 members than to a particular individual, especially where the group is one that is already socially  
4 and politically marginalized.

5

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

10

#### 11 **APPLYING THE REGULATIONS TO A TYPICAL PROTOCOL: ISSUES FOR IRBS**

12

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

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

6

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

16

17 If the research was performed using coded samples, this would allow for a second screen  
18 in which the subset of men whose tissues show a marker for the gene will have their medical  
19 records examined. The same issues about minimal risk apply to this screen, but with a seemingly  
20 greater risk that findings will develop in the course of research that might prompt investigators to  
21 consider communicating their finding to the tissue donors or their physicians. For example, if the

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1 data strongly indicate that those with the markers respond dramatically better to one treatment  
2 than another, investigators may wonder whether it would be best to communicate this information  
3 to patients and their physicians so that the better treatment can be pursued before the patient's  
4 health irreversibly declines.

5

6         At the same time, the tentative nature of these findings, in the view of many, may make  
7 their communication problematic. Since some prostate treatments may have significant side-  
8 effects, such as impotence and incontinence, and since the clinical data on the need to detect and  
9 treat slow-growing prostate cancers in older men is mixed, such tentative findings may put  
10 patients into a position of great uncertainty and anxiety, without the assurance of clinical benefit.  
11 It is the difficulty of understanding the meaning of "minimal risk" with regard to psychosocial  
12 harm (as opposed to physical harm) that makes this issue so complex, and, in turn, makes the  
13 decision about eligibility for expedited review so difficult.

14

15         Psychological risk includes the risk of harm from learning genetic information about  
16 oneself (e.g., that one is affected by a genetic disorder that has not yet manifested itself).  
17 Complicating the issue of communicating genetic information to a subject is that typically the  
18 information is limited to probabilities. Furthermore, genetic data carries with it a margin of error;  
19 and some information communicated to subjects will, in the end, prove to be wrong. In either  
20 event, participants are subjected to the stress of receiving such information. For example,  
21 researchers involved in developing presymptomatic tests for Huntington Disease have been

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1 concerned that the emotional impact of learning the results may lead some subjects to attempt  
2 suicide. They have therefore asked whether prospective participants should be screened for  
3 emotional stability prior to acceptance into a research protocol.

4

5 Note that these disclosures of information can also be beneficial to the subject. One of the  
6 primary benefits of participation in genetic research is that the receipt of genetic information,  
7 however imperfect, can reduce uncertainty about whether participants will likely develop a disease  
8 that runs in their family (and possibly whether they have passed the gene along to their children).

9 Where subjects learn that they will likely develop or pass along the disease, they might plan  
10 differently for the future. To minimize the psychological harms presented by pedigree research, it  
11 would be prudent for IRBs to make sure that investigators will provide for adequate counseling to  
12 subjects on the meaning of any genetic information they might receive. Genetic counseling is not  
13 a simple matter and must be done by persons qualified and experienced in communicating the  
14 meaning of genetic information to persons participating in genetic research or persons who seek  
15 genetic testing.

16

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1           As noted in chapter 3, social risks include stigmatization, discrimination, labeling, and  
2 potential loss of or difficulty in obtaining employment or insurance.<sup>7</sup> Changes in familial  
3 relationships are also among the possible social ramifications of genetic research.

4  
5           Regardless of whether expedited review is permitted by the local IRB or standard review  
6 is required, the IRB may then consider whether subject consent to do the research can be waived.  
7 Once again, the question of minimal risk must be answered. In addition, the investigators would  
8 need to show that doing the research without subject consent is necessary because it is impractical  
9 to contact the donors, and that doing the research without consent will not affect the rights of the  
10 subjects.

11  
12           Given the subtlety of these inquiries, it would not be surprising to find that there is a great  
13 deal of variation in the way IRBs deal with these issues. Some, for example, might find that the  
14 initial screening to identify the subset of samples with markers for the gene ought to be eligible for  
15 expedited review and a waiver of consent, but that subsequent work on the subset ought to

---

<sup>7</sup> For example, an employer who knew that an employee had an 80 percent chance of developing HD in her 40s might deny her promotion opportunities on the calculation that their investment in training would be better spent on someone without this known likelihood. Of course, the company may be acting irrationally (the other candidate might be hit by a car the next day, or have some totally unknown predisposition to debilitating disease), but the risk for our subject of developing HD is real, nonetheless. One problem with allowing third-parties access to genetic information is the likelihood that information, poorly understood, will be misused. Likewise, an insurer with access to genetic information may be likely to deny coverage to applicants when risk of disease is in an unfavorable balance. Insuring against uncertain risks is what insurance companies do; when the likelihood of disease becomes more certain, they may refuse to accept the applicant's "bet."

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1 require full review and subject consent. Others might waive consent for all aspects of the research,  
2 and still others for none.

3

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

14

15         The justification for multiple IRB reviews lies in part in the philosophy of local review to  
16 reflect local standards of human subjects protections, and in part on the expectation that IRBs are  
17 fallible, and that multiple reviews minimizes the possibility of a serious error due to the incorrect  
18 ruling by one particular IRB.

19

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## 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.<sup>8</sup>

### **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, 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.

---

<sup>8</sup> 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.

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1

2           Although groups used different terminology to describe materials, four categories  
3 describing levels of identifiability of human biological materials were discussed in the reviewed  
4 statements. For the purpose of the comparative analysis, the terms describing categories of  
5 human biological materials were adapted from two of the sources to yield the following:<sup>9</sup>

6 **Anonymous** biological materials were originally collected without identifiers or are otherwise  
7 impossible to link to their sources; **Identifiable** biological materials are either directly identified  
8 or coded, such that a subject can be identified either directly or through decoding; such materials  
9 are not now or are not expected to be made anonymous; **Coded** biological materials are  
10 unidentified for research purposes, but can be linked to their sources through the use of a code;  
11 **Directly identified** biological materials are those to which identifiers, such as a name, patient  
12 number, or clear pedigree location, are attached and made available to researchers.

13

#### 14 **When to Require Informed Consent and IRB Review**

15

16           Many groups recommend different protections according to the degree to which samples  
17 used in a research protocol can be identified with a subject. Therefore, how a group defines what

---

<sup>9</sup> 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* 274:1786-1792, 1995.

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1 constitutes identifiable information is important when considering what protections it  
2 recommends. Primarily to gain an understanding of what the various organizations discussed in  
3 terms of the appropriate level of protection, NBAC examined what protections the statements  
4 recommended for permissible use of existing, and permissible future collection and use of human  
5 biological materials. This comparison helped the Commission understand the range of protections  
6 and some innovative ideas for protections that have been discussed by some of these  
7 organizations.

8

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

15

16         Two protections that appear throughout most of the statements, although they are not  
17 applied uniformly, are informed consent and institutional review board (IRB) review. Some  
18 statements provide guiding principles or factors to consider when making decisions about the  
19 appropriate use of materials in research. Others explicitly recommend the application of these  
20 protections to categories that indicate how readily identifiable the sample is.

21

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1           The varied terminology used when professional groups discuss the identifiability of  
2 materials has not contributed to a standardization of practices. Lori Andrews and Dorothy Nelkin  
3 demonstrate an example of the difficulties that arise when terms are not defined or applied  
4 uniformly in the course of a comparison in a recent article. The authors write:

5

6           Because of the risks of research-uses of even *anonymized tissue*, the American Society of  
7 Human Genetics and the American College of Medical Genetics recommend that  
8 individuals be asked whether or not they wish to allow its *anonymous use* before tissue is  
9 taken from them (emphasis added.) (Andrews, 1998)

10

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

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1 in research. In other words, there is no justification for applying the category “anonymous use” to  
2 “identifiable” samples.

3

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

11

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

18

19 The NIH/CDC Workshop does not differentiate between coded or directly identified  
20 samples when applying protections. According to the Workshop participants, Even if the  
21 researcher cannot identify the source of tissue, the samples are not anonymous if some other

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1 individual or institution has this ability” (Clayton, 1995). Accordingly, they propose, “All  
2 research that proposes to use samples that are not now or will not be made anonymous requires  
3 more thorough review.” Thus, with regard to IRB review and informed consent, coded and  
4 directly identified materials deserve equal levels of protection.

5

6         The Pathologists Consensus Statement recommends, with regard to identifiable samples,  
7 that different protections be applied to research using archived, coded samples than to research  
8 using directly identified samples. The statement emphasizes the importance and feasibility of,  
9 “maintaining patient identity and clinical information separate from research data through the use  
10 of coding” (Pathologists, 1997). In this way, they reason, the research use of coded materials  
11 does not pose the same risks to subjects as the use of directly identified materials, and does not  
12 require the same protections. Instead, the statement proposes the following:

13

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

21

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## 1 **Decisions about the Appropriate Use of Existing Samples**

2

3 Many organizations have provided guidelines on how to address some of the difficult  
4 decisions that arise in the course of research using stored materials. These decisions include the  
5 following: (1) when and how to recontact individuals regarding consent for new research uses of  
6 their samples; (2) how to judge the adequacy of previously given consent; and (3) how to assess  
7 protocols that propose to remove identifying information from samples before using them in  
8 research.

9

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

15

16 A statement developed by the National Heart, Lung, and Blood Institute (NHLBI, 1997)  
17 lists several issues for IRBs and funding agencies to consider “[i]n judging the adequacy of a  
18 previous informed consent when an application is received to do new genetic research”: “(1) the  
19 nature of the disease proposed for study, (2) the likelihood that knowing results of the research  
20 will harm or benefit an individual, (3) the availability of effective treatment or prevention for the  
21 disorder, and (4) the burden of such treatment.”

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

7

8           Another complex decision IRBs must address when research with stored samples is  
9 proposed involves judging the appropriateness of removing identifiers from samples. The  
10 NIH/CDC Workshop statement lists five factors for IRBs to consider “in deciding how to assess  
11 protocols that propose to make existing identifiable samples anonymous for use in research”:

12       (1) whether the information the researcher seeks can be obtained in a manner that allows  
13 individuals to consent (this includes the possibility of using tissue samples for which people  
14 had previously given permission for use in research); (2) whether the proposed investigation is  
15 scientifically sound and fulfills important needs; (3) how difficult it would be to recontact  
16 subjects (it is not necessary, however, to prove impracticability); (4) whether the samples are  
17 finite and, if used for research, they may no longer be available for the clinical care of the  
18 source or his or her family (for example, use of tumor samples may be more problematic than  
19 use of transformed permanent cell lines); and (5) how the availability of effective medical  
20 interventions affects the appropriateness of pursuing anonymous research (Clayton, 1995).

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## 1 **Collecting Samples with Appropriate Informed Consent**

2

3           When collecting human biological materials from individuals in a research or clinical  
4 setting, an informed consent process that allows individuals choices regarding how the sample will  
5 be used after the original protocol or procedure, is an important element in the protection of  
6 individuals' interests and facilitation of research. Many organizations have discussed extensively  
7 how to design a manageable informed consent process that would address the individual's  
8 concerns about the present and future uses of his or her sample, and is comprehensible to patients  
9 and research subjects. The types of consent proposed ranged from general consent (consent to  
10 future, unspecified research uses of the material), to layered consent (offers the subject the option  
11 to consent to a variety of classes of research), to specific consent for a unique designated  
12 protocol.

13

14           In some cases the statements offer insightful discussion regarding what level of consent is  
15 appropriate for the use of materials. Regarding general consent, ASHG points out that in certain  
16 instances general consent may be inappropriate, noting that “[i]t is inappropriate to ask a subject  
17 to grant blanket consent for all future unspecified genetic research projects on any disease or in  
18 any area if the samples are identifiable in those subsequent studies.” On the other hand, the  
19 Pathologists Consensus Statement notes that there may be value in requiring general consent  
20 stating, “[t]o give a description of each and every research protocol which might be performed in

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1 the (sometimes distant) future on a patient’s tissue is an unreasonable burden for the patient and  
2 the researcher” (Pathologists, 1997).

3

4 Several statements advocate a form of layered consent for collecting all samples in the  
5 future. NHLBI provides thoughtful discussion on the content of a proposed three-tiered consent.  
6 In such a consent, as NHLBI describes, one is offered the option of consenting to the current  
7 study (first level), a study with goals broadly related to the area of the original study (second  
8 level), and a study with goals unrelated to the area of the original study (third level). (NHLBI,  
9 1997).

10

11 Highlighting the importance of designing adequate informed consent mechanisms in the  
12 future, the National Action Plan on Breast Cancer National Biological Resource Banks Working  
13 Group <sup>10</sup> focuses primarily on future collection and use: “The Working Group believes that when  
14 organizations with access to specimens act according to the following criteria, it should generally  
15 be unnecessary to obtain further consent from patients.” The group acknowledges that its  
16 principles apply to “prospective specimen collection,” and does not make explicit  
17 recommendations for the use of existing samples. However, these carefully developed principles

---

<sup>10</sup> *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.

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1 can be adapted “to allow . . . pathologists to make their collections available for research and, at  
2 the same time, protect the privacy and confidentiality of the tissue sources.”

3

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

14

#### 15 **Additional Protections**

16

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

20

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

11  
12 IRB-approved policies for protecting confidentiality contribute an additional layer of  
13 protection in the research process. Groups such as those endorsing the Pathologists Consensus  
14 Statement have expressed the view that these policies are an important element in any policy  
15 governing the research use of human biological materials that seeks to protect human subjects.  
16 They reason that where these mechanisms are in place, IRBs should be permitted “broader  
17 latitude to waive the requirements for informed consent for research on identifiable (linkable or  
18 coded) samples” (Pathologists, 1997).

19  
20 The effectiveness of institutional confidentiality policies is central to any system where  
21 masking individuals’ identities by coding samples is used as a way of protecting privacy and

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1 maintaining confidentiality. The Association of American Medical Colleges (AAMC) describes  
2 the importance of maintaining access to patient information through the use of coding  
3 mechanisms:

4  
5 A great deal of contemporary research is dependent on the ready accessibility of  
6 personally identifiable, i.e., linkable, archival patient materials, such as medical records and  
7 tissue specimens removed in the course of routine medical care . . . . As a rule, these kinds  
8 of studies [epidemiologic and health services research] do not require that the identity of  
9 the patient be known to the investigator. But in the great majority, the investigators must  
10 have the ability to obtain additional, or follow up information about particular sets of  
11 subjects in order to evaluate the significance of the findings and interpret them in an  
12 appropriate biological, clinical or epidemiological context. The only way such additional  
13 information can be gathered in studies of archival patient materials is if the materials are  
14 coded in such a way that they remain permanently linkable to specific patients (AAMC,  
15 1997).

16  
17 The AAMC also proposes one way that secured access to such information could be  
18 maintained:

19  
20 One possible approach to this task would be to give each patient at his/her first encounter  
21 with the health care system two unique identifiers, one for clinical use, the other for

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

4  
5 In sum, professional groups varied in the way they defined the categories of anonymity of  
6 samples and the protections recommended for each category. Several have developed guidelines  
7 for IRBs and investigators as they confront the questions that arise when research is proposed  
8 using existing materials. Finally, these statements contained some but not explicit discussion  
9 about the mechanisms for ensuring the materials are stored and/or used in such a way that the  
10 confidentiality of the source of the material is promoted.

11

## 12 **INTERNATIONAL GUIDELINES**

### 13 **[To be developed]**

14

15 The Ethics Committee of the Human Genome Organisation (HUGO) is unique in placing  
16 primacy in its recommendations concerning the use of stored materials in research on the  
17 following two factors: (1) “the source of the sample, that is, whether it was collected during  
18 routine medical care or during a specific research protocol . . .”; and (2) whether there was, at  
19 the time the sample was collected, “general notification” of the institution’s policy concerning  
20 future uses of samples. Of the categories of materials it defines, the HUGO Ethics Committee  
21 recommends the most stringent protection for the research use of “routine samples, obtained

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1 during medical care and stored . . . before notification of such a policy” (HUGO, 1998). Such  
2 samples may only be used if, provided there is ethical review, they have been anonymized prior to  
3 use. All other samples may be used if, again provided there is ethical review, the patient or  
4 participant “has not yet objected, and the sample to be used by the researcher has been coded or  
5 anonymized.”

6

7 **OTHER CONSIDERATIONS: MEDICAL RECORD PROTECTION AND HUMAN SUBJECTS**

8 **RESEARCH**

9

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

19

20 The federal regulations that govern human subjects research apply to the use of medical  
21 records. Efforts to link one record with another, or to link a record with an interview of the

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1 patient, can be considered “research” under the federal definitions. If the records have any  
2 personal identifiers, then this constitutes human subjects research and requires IRB review and  
3 patient/subject consent, subject of course to the same exceptions outlined above for research on  
4 the patient/subject. Indeed, the regulations governing tissue use and medical record use are  
5 basically the same and on a practical level treat tissue as simply another form of a medical record.

6

7         However, no federal law protects the privacy of medical records, unless the records are  
8 actually held by the government, and it has been noted that the areas to which Congress has  
9 chosen to extend privacy protection—including credit protection,<sup>11</sup> electronic communications<sup>12</sup>,  
10 and video rental lists<sup>13</sup> —provide a dramatic contrast to the lack of a federal law covering the  
11 confidentiality of privately-held medical records.

12

13         On the other hand, there are more general rules, both statutory and common law, that lay  
14 the groundwork in many states for a claim of invasion of privacy for nonconsensual use of medical  
15 records. Indeed, nearly every state has laws or regulations that provide varying degrees of  
16 protection for information contained within medical records.<sup>14</sup> Many states have recently adopted  
17 privacy statutes, frequently in the context of protecting the confidentiality of records regarding

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<sup>11</sup> See Fair Credit Reporting Act of 1970, Pub. L. No. 91-508, 84 Stat. 1114 (codified as amended at 15 U.S.C. section 1681 (1988)).

<sup>12</sup> See Omnibus Crime Control and Safe Streets Act of 1968, tit. III, the Electronic Communications Privacy Act of 1968, Pub. L. No. 90-351, section 802, 82 Stat. 212 (codified as amended at 18 U.S.C. sections 2510-2521 (1988)).

<sup>13</sup> See Video Privacy Protection Act of 1988, Pub. L. No. 99-508, 100 Stat. 1860 (codified at 18 U.S.C. section 2701 (1988)).

<sup>14</sup> Robert E. Smith, *Compilation of State and Federal Privacy Laws* (1992).

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1 certain diseases, most often HIV/AIDS, and various mental illnesses.<sup>15</sup> In most instances, these  
2 acts are aimed at preventing the misuse of such personal medical information by insurance  
3 companies and employers, and thereby protecting the individual from discrimination and/or  
4 stigmatization. The variability of state law protections has been cited as a problem in itself,  
5 regardless of the privacy protections offered by the states.<sup>16</sup>

6

7         Where statutes exist, they may specifically contemplate access to medical records for  
8 research use. For example, California's medical records confidentiality law, for example, states  
9 that the "information may be disclosed to public agencies, clinical investigators, health care  
10 research organizations, and accredited public or private nonprofit educational or health care  
11 institutions for bona fide research purposes. However, no information so disclosed shall be  
12 further disclosed by the recipient in any way which would permit identification of the patient."<sup>17</sup>

13 This section exempts releases of medical information for bona fide research purposes from the  
14 law's general requirement of patient authorization for any release.

15

16         The California law defines "medical information" as "any individually identifiable  
17 information in possession of or derived from a provider of health care regarding a patient's

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<sup>15</sup> 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.

<sup>16</sup> Marianne Lavelle, Health Plan Debate Turning to Privacy, Nat'l L.J., May 30, 1994, at A1.

<sup>17</sup> Cal. Civ. Code Ann. § 56.10 (c)(7) (West 1982 & Supp. 1998).

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1 medical history, mental or physical condition, or treatment,”<sup>18</sup> language which is very similar to  
2 that of the Common Rule. Finally, it is interesting to note that California separately addresses  
3 disclosure of genetic test results contained in an “applicant or enrollee’s medical records” by a  
4 health care service plan. The law forbids disclosure by a health care service plan of “results of a  
5 test for a genetic characteristic to any third party in a manner that identifies or provides identifying  
6 characteristics of the person to whom the test results apply, except pursuant to a written  
7 authorization.”<sup>19</sup>

8

9 Florida and Minnesota laws also specifically address the use of medical records in  
10 research. Florida’s general medical record confidentiality statute states that records “may not be  
11 furnished to, and the medical condition of a patient may not be discussed with, any person other  
12 than the patient or the patient’s legal representative or other health care practitioners and  
13 providers involved in the care or treatment of the patient, except upon written authorization of the  
14 patient.”<sup>20</sup> However, as in California, such records may be furnished without written authorization  
15 “[f]or statistical and scientific research, provided the information is abstracted in such a way as to  
16 protect the identity of the patient or provided written permission is received from the patient or  
17 the patient’s legal representative.”<sup>21</sup>

18

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<sup>18</sup> *Id.* § 56.05(b).

<sup>19</sup> *Id.* § 56.17.

<sup>20</sup> Fla. Stat. § 455.667(5) (1997).

<sup>21</sup> *Id.* § 455.667(5)(d).

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1 In Minnesota,

2 [a] provider, or a person who receives health records from a provider, may not  
3 release a patient's health records to a person without a signed and dated consent from the  
4 patient or the patient's legally authorized representative authorizing the release, unless the  
5 release is specifically authorized by law. . . . [A] consent is valid for one year or for a lesser  
6 period specified in the consent or for a different period provided by law.<sup>22</sup>

7  
8 An exception to Minnesota's general rule is that health records "may be released to an  
9 external researcher solely for purposes of medical or scientific research." The State allows the  
10 release of health records generated before January 1, 1997 if the patient has not objected or does  
11 not elect to object after that date; in contrast, the State requires that, for health records generated  
12 on or after January 1, 1997, the provider must:

13 (i) disclose in writing to patients currently being treated by the  
14 provider that health records, regardless of when generated, may be  
15 released and that the patient may object, in which case the records  
16 will not be released; and

17  
18 (ii) use reasonable efforts to obtain the patient's written general  
19 authorization that describes the release or records in item (i), which

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<sup>22</sup> Minn. Stat. § 144.335 subdivision 3a (1997).

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

3  
4 Further, in making a release for research purposes, the provider must make a reasonable  
5 effort to determine that:

6 (i) the use or disclosure does not violate any limitations under which the record  
7 was collected;

8 (ii) the use or disclosure in individually identifiable form is necessary to  
9 accomplish the research or statistical purpose for which the use or  
10 disclosure is to be made;

11 (iii) the recipient has established and maintains adequate safeguards to protect  
12 the records from unauthorized disclosure, including a procedure for removal  
13 or destruction of information that identifies the patient; and

14 (iv) further use or release of the records in individually identifiable form to a  
15 person other than the patient without the patient's consent is prohibited.

16  
17  
18 In addition to these and other existing statutes, there are over 150 pending state legislative  
19 initiatives addressing the use of medical information.<sup>23</sup> Many of these initiatives attempt to  
20 protect an individual's privacy interest by preventing the dissemination of personal

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<sup>23</sup> 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; 1997 DE S.B. 153;

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1 information—doing so by restricting the ability of those who hold medical records, such as  
2 hospital pathology laboratories, to give out information from the records, and by restricting the  
3 ability of investigators to conduct such research except in certain circumstances.

4

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

15

16         Finally, many legislative initiatives prohibit research facilities from obtaining or retaining  
17 samples for genetic testing unless the source of the sample has given consent or the sample is used  
18 in anonymous research. A few states are considering or have considered bills that provide the  
19 source of the sample with greater control over its uses by giving the source a legal property right

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1 in the sample and information that is derived therefrom.<sup>24</sup> To date only one state has passed such  
2 a provision into law, and the property right it grants does not address the source's ability to profit  
3 monetarily from the sample<sup>25</sup>

4  
5 What appears clear from the state legislative initiatives is that there is a perceived need to  
6 protect medical information from possible negative consequences of research conducted on  
7 human biological materials. This need is particularly pronounced where the information may  
8 identify the individual.

9  
10 Courts have only recently begun to recognize individual "privacy" rights with respect to  
11 one's medical records. Early cases viewed unauthorized disclosure as a form of breach of  
12 statutory duty, libel, malpractice, breach of trust, and breach of contract. The language in early  
13 cases from that era is quite strong in its condemnation of what it deemed a valid claim for  
14 unauthorized revelation of medical secrets. For example, the New York case stated: "Despite the  
15 fact that in no New York case has such a wrong been remedied, due most likely to the fact that so  
16 few physicians violate this fundamental obligation, it is time that the obligation not only be  
17 recognized but that the right of redress be recognized as well."<sup>26</sup> More recently, the United States  
18 Court of Appeals for the Third Circuit recognized a form of a privacy right against the  
19 government's request for access to medical records in order to investigate alleged health

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<sup>24</sup> See e.g., 1998 UT H.B. 271; 1997 MI H.B. 5459.

<sup>25</sup> Oregon's statute addressing an individual's rights in genetic information, ORS @ 659.715 (1997).

<sup>26</sup> 93 Misc. 2d 201 (N.Y. Sup. Ct. 1977).

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1 hazards.<sup>27</sup> The court balanced this “right” against seven factors:

2

3 the type of record requested, the information it does or might contain, the potential for  
4 harm in any subsequent nonconsensual disclosure, the injury from disclosure to the  
5 relationship in which the record was generated, the adequacy of safeguards to prevent  
6 unauthorized disclosure, the degree of need for access, and whether there is an express  
7 statutory mandate, articulated public policy, or other recognizable public interest militating  
8 toward access.

9

10 In that particular case, the court held that "the public need prevailed over the claim that  
11 medical records in general were protected from discovery." Of course, it is not necessarily true  
12 that all courts conducting this type of analysis would grant investigators access to medical records  
13 despite asserted privacy rights.

14

15 More recently, the Second Circuit found that an individual has a constitutional right to  
16 privacy in his HIV status “because his personal medical condition is a matter that he is normally  
17 entitled to keep private.”<sup>28</sup> Again, it is unclear how this would apply in a medical research setting,  
18 but it is significant for its explicit reliance on constitutional levels of protection for one’s right to

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<sup>27</sup> United States v. Westinghouse Electric Corp., 638 F.2d 570 (3d Cir. 1980).

<sup>28</sup> Doe v. City of New York, 15 F.3d 264 (2d Circuit, 19--).

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1 keep medical information private. Finally, in some jurisdictions, state constitutional provisions  
2 offer privacy protection <sup>29</sup>

3

#### 4 **CONCLUSIONS**

5

6 In its deliberations, NBAC reviewed the applicability of the existing federal regulations  
7 pertaining to research with human biological materials. The Commission identified some notable  
8 ambiguities. First, the current regulations do not make completely clear what is meant by  
9 “identifiability” when determining whether in fact a human subject is involved in research on  
10 biological samples. Thus, there is resulting confusion about whether certain research is covered  
11 (based on how closely the samples are linked to their sources and how easily that linkage can be  
12 accomplished). The issue of identifiability is further confounded by the researcher’s growing  
13 ability to identify the source (even when unidentified) because of the uniqueness of the clinical  
14 information that accompanies the material when it is delivered from the repository.

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<sup>29</sup> 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; N.Y. Const. art. I, section 12; S.C. Const. art. I, section 10; Wash. Const. art. I, section]. Generally, they require that state action must have caused the violation for protections to apply[7. See, e.g., Me. Rev. Stat. Ann. tit. 17-A, section 511 (West 1983); Mass. Gen. Laws Ann. ch. 214, section 1B (West 1986); Neb. Rev. Stat. section 20-201 to -211 (1991); R.I. Gen. Laws section 9-1-28.1 (1985); Utah Code Ann. section 76-9-401 (1990); Wis. Stat. Ann. section 895.50 (West 1983)]. California's constitutional privacy right is more explicit; private parties can apply it to privacy infringements. [Cal. Const. art. 1, section 1.]

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1           Second, the existing regulations are silent on the topic of group or community harm.  
2           Thus, protocols that pose insignificant risks to individuals but might implicate strong group  
3           interests do not get special IRB attention. This has implications for groups such as kindreds or  
4           ethnic and racial subpopulations as well as collectivities of individuals who share a common trait,  
5           such as a genetic condition or disease status.

6

7           Third, the regulations offer insufficient guidance on the meaning of “minimal”  
8           psychosocial risk or the nature of the subjects’ “rights and welfare” to be protected.

9

10           Fourth, the existing regulations do not make clear the status of living relatives of deceased  
11           individuals whose stored samples are used in research. Although OPRR has indicated that these  
12           people might in fact be considered human subjects by virtue of their genetic relationship to the  
13           sample source, the regulations do not specify how this consideration is to be handled by IRBs.

14

15           Fifth, there are major unresolved issues pertaining to the on-going access to medical  
16           records that have significant implications for research using human biological materials.

17

18           Despite the fact that the current regulations appear to apply in most cases, other issues  
19           pertaining to adequate protections arise. For example, provision of informed consent is a required  
20           but insufficient protection of both the interests of the research subject and the investigator.

21           Moreover, there might be overriding state laws that apply regarding the research use of medical

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1 records, thereby limiting the ability of researchers to gather unlimited information from individuals  
2 whose names are linked to the biological material.

3

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

7

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