Appendix D: 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.[1] In particular, this analysis assisted the Commission in understanding how its recommendations might compare to those of other groups. The comparison was not initiated to assess or evaluate the strengths or weaknesses of any statement.

Definitions: What Constitutes "Identifiable" Information?

The concept of anonymity is one source of complexity in discussing appropriate use of human biological materials. As discussed in chapter 4, 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

[1] Fourteen statements, published and widely discussed in the literature, or available on the World Wide Web, were reviewed.

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

A source of consistency that aided comparison of statements, was that all organizations categorized materials using the same method: the degree to which the samples as stored are able to be identified as coming from a particular individual.[2] Nonetheless, different terms describing categories of materials are used across statements and, where the same terms are used, they are not defined in the same manner.

Although different terms were applied to label the categories, four categories describing levels of identifiability of human biological materials were discussed in these 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:[3] **Anonymous** (unidentified) biological materials were originally collected without identifiers or are otherwise impossible to link to their sources; **Identifiable** (unlinked) 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** (identified) biological materials are those to which identifiers, such as a name,

[2] No statements provide explicit justification for this method of categorization.

[3] 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.

patient number, or clear pedigree location, are attached and made available to researchers.

An example of the difficulties that arise when terms are not defined or applied uniformly in the course of a comparison is demonstrated in a recent article by Lori Andrews and Dorothy Nelkin. The authors write:

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

Some Recommended Human Subjects Protections

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 often influences what protections it recommends. Having identified and defined the categories of materials that would be used in comparing the statements, NBAC examined what protections the statements recommended for permissible use of existing, and permissible future collection and use of human biological materials. This was done primarily to gain an understanding of what the various organizations discussed in terms of the appropriate level of protection for research using human biological materials. As well as providing NBAC with an understanding of the range of protections discussed, the comparison also revealed 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 statements do not explicitly address protections for permissible use of existing materials, but instead provide principles for applying protections when materials are collected 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 appropriate use of materials in research. Others explicitly recommend the application of these protections to "information" categories of the research analysis of human biological materials.

For those statements that use the latter approach, an obvious source of variation in recommending the application of protections is different understandings of whether coded samples should be considered identifiable. Some statements use "identifiable" to 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 usages 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 "information" category of human biological materials. 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, when recommending IRB review and informed consent, coded and directly identified materials are treated as requiring equal levels of protection.

The Pathologists Consensus Statement recommends 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.

The Ethics Committee of the Human Genome Organisation (HUGO) is unique in placing primacy in its recommendations concerning the use of stored materials in research on the following two factors: (1) "the source of the sample, that is, whether it was collected during routine medical care or during a specific research protocol . . ."; 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 only be used if, provided there is ethical review, they have been anonymized prior to use. All other samples 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."

Instead of explicitly recommending protections, some statements provide guidelines for making decisions about appropriate use of 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."

When it is determined that it would be inappropriate to use samples without contacting individuals, the statement 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).

The NIH/CDC Workshop statement, addressing the use of existing identifiable samples, 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).

A statement developed by the National Heart, Lung, and Blood Institute (NHLBI, 1997) also addresses the appropriate use of existing samples by providing guidelines for decision-making rather than advocating specific protections. It 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."

Recommended protections for future collection of human biological materials vary among the statements. For example, the statements put different emphasis on informed consent. 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 PRIM&R/ARENA Tissue Banking Working Group[4] statement is unique

[4] *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.

among the analyzed statements in focusing 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 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 IRB review and informed consent, some organizations discussed ideas for other protections. NHLBI outlines 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).

Some statements recommend that institutions that store and/or distribute human biological materials have in place IRB-approved policies for protecting confidentiality. Groups such as those endorsing the Pathologists Consensus Statement, reason that these policies are an important element in any policy governing the research use of human biological materials that seeks to protect human subjects.

Statements that discuss institutional confidentiality policies tend to emphasize the importance of permitting investigators access to updated clinical information associated with human biological materials. The Association of American Medical Colleges (AAMC) describes the importance of maintaining access to such information:

> 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).

Statements that emphasize the importance of institutional confidentiality mechanisms are less likely to recommend protection in the form of IRB review and informed consent. They are more likely, however, to contribute to a discussion of confidentiality mechanisms. With such mechanisms in place, the Pathologists Consensus Statement reasons, IRBs should be permitted "broader latitude to waive the requirements for informed consent for research on identifiable (linkable or coded) samples" (Pathologists, 1997).

In sum, all statements used a similar method of categorizing research on human biological materials, a method based on the degree of identifiability of the materials as stored. The statements varied in the way they defined the categories of anonymity of samples and the protections recommended for each category. 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 GUIDELINES

[To be written]

A number of other countries have addressed this issue through bodies similar to NBAC

They have identified similar issues.

Local rules may differ.