Special Article

New Challenges for Biomedical Research Utilizing Human Biological Materials

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After much anticipation, the National Bioethics Advisory Commission (NBAC) recently released its report and recommendations on research involving human biological materials.¹ The NBAC is the latest in a series of commissions and committees that have been convened by Congress or the federal government to address ethical concerns about the practice of biomedical research, usually following dramatic scientific and medical advances or scandals concerning abuses of human subjects involved in research. In the case of the NBAC, which was established by Executive Order 12975, signed by President Clinton in 1995, the immediate precipitating cause was a scandal that came to light involving the irradiation of patients in the 1950s without their knowledge or informed consent.

One of the first issues considered by the NBAC was the use of human biological materials in research. This was in large part due to a concurrence of events including a) advances in the ability to amplify DNA from minute amounts of virtually all human biological materials, including archived fixed and frozen samples; b) the expected complete elucidation of the human genome; and c) increased use of computerized databases of patient information. These events led to a growing concern of the public, including ethicists, scientists and physicians, legislators, and patient advocates, about the purposeful or inadvertent use of human samples in research to detect genetic profiles of individuals.²

Historically, the concept of informed consent arose from the common law tort of battery, ie, an individual has the right to be protected from nonconsensual touching. In the 1950s, in the United States, the courts began to examine the quality of the consent. Failure to obtain informed consent could lead to a finding of negligence and malpractice. To a great extent, this new sensitivity was the result of the Nuremberg Code,³ possibly the most important document in the history of the ethics of medical research.⁴ The Code was formulated in 1947 and focused on voluntary consent and the human rights of research subjects. The Code not only required that phy-

sicians and researchers protect the best interests of their subjects, but also importantly gives the subjects the same authority as the physician/researcher to end the experiment before its conclusion. To a great extent, the Nuremberg Code established a fundamental change in the Hippocratic doctor-patient relationship.⁴ In the latter, once they have agreed to be treated by the physician, patients trust the physician to act in their best interest and play a relatively passive role. However, the Nuremberg Code stresses that such trust may be misplaced in the research setting because the primary goal of the physician conducting a research study is to test a scientific hypothesis by following a protocol, and the physician may not adequately appreciate the risks to research subjects.

Although the Nuremberg Code has not been officially adopted in its entirety by any nation or medical association, its basic principle of informed consent is now universally accepted and provides the ethical underpinnings of current regulations that govern research throughout the world. In the United States, human subjects are currently protected from research risks by both state and federal laws. The so-called "Common Rule" is a series of federal regulations that apply to research studies funded by 16 federal departments and agencies. The regulations of the Common Rule are set forth by the Office for Protection from Research Risks (OPRR) in the Code of Federal Regulations (CFR), Title 45, Part 46. In addition, the Food and Drug Administration has similar regulations that are detailed in CFR, Title 21, Part 312. In general, the regulations for protection of human subjects call for voluntary informed consent of human subjects and oversight of each research protocol and the consent process by a local Institutional Review Board (IRB). The IRB is charged with providing an independent review of the risks and benefits of each research proposal and with monitoring whether informed consent is necessary and sufficient. Although the Common Rule regulations technically apply only to research studies funded by the

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participating federal agencies, the OPRR has entered into multiple project assurances with almost all academic medical institutions in the United States that accept federal funds for research. Through the multiple project assurances, the institutions have agreed to be responsible that all research involving human subjects that is conducted within the institution, whether or not that research specifically receives federal funding, will comply with the Common Rule regulations. The Common Rule regulations, as well as access to other relevant biomedical ethics documents, are available online at <http://grants.nih.gov/grants/oprr/oprr.htm>.

The Common Rule guidelines were formulated as an outgrowth of the Belmont Report⁵ of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The latter commission was mandated by Congress in 1974, soon after public disclosure of the notorious Tuskegee-syphilis experiments, to provide an ethical foundation for a system of protections for human subjects. The Belmont Report identified three basic ethical principles relevant to research involving human subjects: a) respect for persons (personal autonomy); b) beneficence; and c) justice. Respect for persons means that individuals should be treated with respect to their personal autonomy. Subjects should enter into research studies voluntarily and with sufficient information to make an informed choice. The basic principle of beneficence refers to protection from harm as well as to efforts to secure the well-being of individuals. Efforts should be made to maximize possible benefits and to minimize possible harms in the conduct of human subjects research. Justice refers to a sense of fairness in sharing risks and benefits of research. In other words, research should not involve groups that are unlikely to be beneficiaries of the research, and all elements of society should be offered the opportunity to participate in, and benefit from, research. Furthermore, subjects should not be selected because of vulnerability, manipulability, or compromised position.

The Common Rule applies to research involving human subjects, including the use of tissue samples and other human biological materials. Human subjects are involved if there is an intervention or interaction with a living person and/or their tissue samples that would not be occurring (or that would be occurring in some other fashion) if it were not for the research. Deceased persons are not human subjects according to this definition, and therefore research involving biological materials from persons who are now deceased is not considered to be human subjects research. Nor are human subjects considered to be involved when no identifiable private data or information will be obtained in a form that could be associated with the individual.

In some cases, a research study involving human subjects may be exempt from the Common Rule regulations. The inclusive requirements for exemption are that a) the study uses only data or specimens that existed before the inception of the research study and b) the data or specimens are "publicly available" or the information will be recorded by the investigator in such a way that it cannot be linked to the subject. The meaning of "publicly avail-

able" is not clear to many investigators. Although some investigators have taken a broad definition of "publicly available" to include samples and cell lines derived from human specimens that can be obtained by scientists from tissue culture and tissue repositories, others use a much narrower definition that excludes cell lines from repositories (since the cell lines are not generally accessible to the lay public) and include only information such as any member of the public may find in a source such as the phone book. Exemptions should be approved by either an Institutional Review Board or by another designated office of the institution.

The OPRR considers that human biological materials are either unidentified or identified. Unidentified samples include anonymous samples that have never been attached to an identifier such as a name, a social security number, a chart number or a departmental tracking number. In addition, anonymized samples that are rendered anonymous by irreversibly stripping identifiers are usually considered unidentified. Anonymous and anonymized samples can be associated with demographic and clinical information that was available at the time of collection or anonymization as long as the attached information cannot lead to the identification of the subject.

According to current OPRR interpretation, identified samples include not only those in which a specific identifier is included with the specimen, but also "linked" or "coded" samples that have a random alphanumeric code but can be potentially linked to their sources through use of a key to the code. Many investigators have assumed incorrectly that research on linked materials is exempt from IRB review because they themselves do not have ready access to the key, and are using the samples in an anonymous manner.⁶ Many research groups have proposed that archived linked samples be considered like anonymized samples since they are used in an unidentified manner by the researcher.⁷ One potential consequence of the inclusion of linked samples with identified samples, is that some researchers may be tempted to anonymize samples to avoid the regulatory burden of IRB review. However, when the link to a key that provides identifiers is broken, the translational significance of the research may be diminished, since updated clinical information is no longer available. Therefore, prognostic significance, treatment effectiveness, and other outcome-related results of the investigation may be lost. However, current OPRR guidance includes linked samples with identified samples, since if the key exists anywhere, even in another institution, the potential exists for identification of the source.

Therefore, research studies using linked and identified samples are subject to IRB review and investigators must provide evidence of informed consent for use of the human tissues in the proposed research study. The IRB can grant a waiver of the informed consent requirement if the research poses a minimal risk, respects personal rights, and if it would be impractical to obtain consent. The definition of "impractical" is not precise. Although some IRBs have interpreted this to mean that it would be impractical to find and re-contact the sources of archived samples that were collected over a long span of time, and

have granted a waiver, other IRBs have stated that time and money should not be an impediment to obtaining consent.

In general, the NBAC report on use of human biological materials in research studies supports the current Common Rule of federal regulations as well as current guidance by the OPRR¹ concerning the grouping of linked samples with identified samples. Although without legal standing, there is little doubt that the NBAC report will strongly influence the way institutions and IRBs will process and review research proposals involving the use of human biological materials. The NBAC report discourages unlinking of samples to avoid the regulatory burden of IRB review, especially if the value of the research will be reduced. Furthermore, it recommends that someone other than the investigator be responsible for coding samples, thus introducing a third party into the chain of tissue handling. The NBAC report uses a narrow definition of "publicly available" and recommends that in most cases, the exemption from the Common Rule for studies using specimens from repositories of human biological materials would not apply. Thus, the number of studies overseen by IRBs would increase.

The NBAC report also strongly recommends an improvement in the informed consent process, including a separation of obtaining consent to research use of human biological materials from obtaining informed consent to clinical procedures. It further recommends that research consent forms provide potential subjects with several options, ranging from complete refusal for use of their tissues in research, through a series of limited permissions, up to permitting coded use of their biological materials for any kind of future study. Implementation will require institutions to quickly and expeditiously revise the current consent process. Furthermore, the NBAC report raises the concern that general releases for research given in conjunction with a clinical or surgical procedure should not be presumed to cover all types of research over an indefinite period of time. It charges investigators and IRBs to review existing consent documents to determine whether the subjects anticipated and agreed to participate in the type of research proposed. Investigators may have to re-contact subjects and obtain new consent for current research on already archived samples. In such cases, however, the NBAC report urges the IRBs to presume that it would be impracticable to meet the consent requirement. In addition, investigators and IRBs should consider potential harms to not just the individuals from whom the samples have been taken, but also to groups associated with the individual. Potential risks to specific groups should be disclosed during any required informed consent process.

The recommendations potentially increase the regulatory burden on investigators and IRBs. On the other hand, the NBAC report also recommends that IRBs be flexible in assessing minimal risk research involving linked human biological materials, and that such minimal risk studies should be eligible for expedited IRB review. Furthermore, the report recommends that IRBs should operate on the presumption that research on coded samples is of

minimal risk and therefore may be eligible for consideration of a waiver of the informed consent rule.

It is clear that the standards by which we currently judge the informed consent process and the use of human biological materials in research have changed over the past decades.⁸ Consent procedures that were developed just a few years ago may not meet today's needs, and it is not clear how accurately we can predict the needs of the next decade and century. The NBAC report presents new challenges to biomedical researchers who need to use human biological materials in their research. Some of the recommended changes in the consent process may complicate the ability to implement new technological advances, such as the use of tissue microarrays which use thousands of archived samples that may have been collected from many institutions over a long period of time.

It will take some time to assess whether the NBAC report's recommended policies will achieve an appropriate balance between protecting individuals' rights and providing sufficient flexibility to researchers so that biomedical research can continue to benefit the public health. Regulatory bodies should consider that limiting access of human biological materials to researchers may indirectly limit the choice of individuals to benefit from biomedical research. Some have warned that the altruistic contribution of the citizen to the public health is being supplanted by a thought process in which the tissue sample takes on a life and a legal personality of its own.⁹ Town meetings held by the NBAC show that to a great extent, the public wants to participate in research and approves of the use of their tissues, as long as they are informed about the future use of their samples and confidentiality and privacy policies are in place.¹ It has been stressed by several groups that the potential danger is not in the use of human tissues but in the misuse of the information gathered from the research.⁷ It is therefore critical that all institutions develop strong confidentiality and privacy policies to guarantee the safe use of human biological materials in research. It is also incumbent on all investigators using human biological materials to become familiar with current state and federal regulations, to be in close contact with their IRBs so that their proposals and prospective consent forms meet current expectations, and to educate the public about the risks and benefits of research using human biological materials.

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