

Consensus Statement

Informed Consent for Genetic Research on Stored Tissue Samples

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Objective.—To develop recommendations for obtaining adequate informed consent in the future when gathering tissue samples that may be used for genetic studies and defining the circumstances under which it is necessary to obtain further consent if tissue samples already in hand are to be used for such research.

Participants.—Scientists, ethicists, lawyers, and consumers selected by the National Center for Human Genome Research and the Centers for Disease Control and Prevention to represent a wide array of opinions.

Evidence.—Statutes, regulations, and cases and articles on law and ethics.

Consensus Process.—Initial workshop, followed by circulation of several drafts of this document with opportunities for comment by workshop participants and others as well as smaller meetings involving participants with widely differing views.

Conclusions.—Genetic research using stored tissue samples poses an array of benefits and risks to individuals, researchers, and society. As a result, the workshop participants conclude that (1) informed consent is required for all genetic research using linkable samples unless conditions for limitation or waiver are met; (2) informed consent is not required for genetic research using anonymous samples but may be considered if identifiers are to be removed from currently linkable samples; (3) institutional review boards could usefully review all protocols that propose to use samples for genetic research; and (4) further work regarding these issues is warranted.

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A WORKSHOP consisting of scientists, ethicists, lawyers, and consumers was convened jointly by the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) on July 7 and 8, 1994, at the NIH to develop recommendations for securing appropriate informed consent when collecting tissue samples for possible use in genetic research and for defining indications for additional consent if samples in hand are to be used for genetic studies. The analysis that follows represents the consensus of the individuals listed at the end of this

document (although not all signers agreed with every point) and is not official policy of the NIH and the CDC. The conclusions herein were reached after consideration of many drafts and several smaller meetings. This document is meant to guide the deliberations of investigators who design research projects as well as for the institutional review boards (IRBs) and study sections that review proposed projects.

See also pp 1783 and 1806.

A constellation of forces made it desirable to reexamine what the current regulations for the protection of human subjects require and to engage in more general ethical discussion, asking whether these regulations adequately reflect both the desirability of pursuing research and the concerns of individuals or whether there is need for change. (Since this project began, others^{1,2} have also proposed solutions to these problems.) As we decide how best to pursue genetic research and the improvements in health and well-being that we hope will follow, both the benefits that improved knowledge can bring to individuals in the future and the cur-

rent concerns that some individuals have about this research must be considered. As evidence of this sort of balancing, it is widely accepted that informed consent must be obtained for the many projects that involve the direct prospective involvement of individual subjects. The role of informed consent has been much less clear for research that does not require such personal involvement but rather can be performed using tissue samples. At present, much genetic research requires only DNA, which can be isolated from any nucleated cell. In this article, the term *tissue sample* will include all samples that can serve as DNA sources, including not only solid tissues, but also blood, saliva, and any other tissues or body fluids containing nucleated cells. Genetic variability among individuals, as evidenced by genetic polymorphisms, is often studied using population-based samples. Efforts to establish relationships between genotypes and phenotypes can use samples that may reside in single-disease registries, individual investigators' collections, or in more general collections, such as surgical pathology collections.

People may not understand, however, that tissue samples they provide may be used for genetic research. They may have had any of a variety of reasons for providing the tissue—for medical screening and diagnostic testing, for tests following surgical procedures, and for clinical and epidemiologic research focusing on individuals, families, or populations—some of which are unrelated to the research in which the samples are used.³ Patients may expect that tissue samples will be used only for tests to provide information for their medical care. They may believe that samples will be discarded after testing, although the law often requires that samples be retained. When samples are obtained as part of medical care, patients may not be told about the possibility that these samples will be stored and used for research. In some relatively rare situations, such as state-mandated newborn screening, patients or those who make health care decisions for them may be unaware that tissue samples have been obtained.⁴

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A complete list of workshop participants who support the document appears at the end of this article.

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Even though research subjects generally are informed about the scope of the immediate project, one investigator^{5,6} has found that documents used to obtain informed consent in genetic research usually do not inform subjects that the samples they provide may be retained and used for research well into the future, including research on disorders unrelated to those for which the subjects originally provided their samples and by investigators at other institutions. In the absence of such disclosure, subjects may assume that such storage and later use will not occur.

There is also a growing understanding that genetic information may be particularly sensitive and that some people may not want to have genetic information about them obtained, particularly if it is revealed either to themselves or to others. In addition, people who are studied in research projects may wish to be regarded more as collaborators rather than as subjects. The weight given to such concerns in deciding how best to pursue research may change over time as society's understanding of research ethics evolves.

THE NEED TO OBTAIN INFORMED CONSENT FOR RESEARCH

Increasing the fund of knowledge generally is a good both for society and for the individuals whose care is improved by more complete understanding. Society rightly values research and the contributions of those who participate as subjects in research. But despite the desirability of increased knowledge, research can risk harming the individuals who are being studied. As a result, the general legal and ethical rule is that people participate in research only after they have given their informed consent.

What functions does informed consent serve in research? From the perspective of the individual, the disclosure required for consent appraises prospective subjects about the nature of the project and about the risks and benefits that accompany participation so that they can decide whether to participate. If they choose to take part, they will know what to expect and may have the opportunity to take steps to avail themselves of the benefits or to avoid or ameliorate the risks.⁷ People who choose to participate may also feel good about the altruism inherent in their decision.

Obtaining informed consent also serves the interests of researchers by reducing the risk that subjects will pursue legal actions when their expectations about the research are not met. The possibility of unhappiness and even litigation later on may be greatly reduced by early disclosure, discussion, and the opportunity to

refuse to participate. Finally, seeking consent from prospective subjects serves important societal interests. Demonstrating respect for persons and avoiding harm are important principles in our society. Beyond that, society benefits from the communal commitment embodied in an individual's knowing decision to participate in research. Public commitment to obtaining consent for research promotes the willingness of people to seek medical care because patients can be reassured that they do not give up their right to decide whether to participate in research when they enter the health care system.

Yet obtaining consent entails costs. Federal law has long defined conditions under which research can be undertaken without obtaining consent, reflecting an assessment that in some settings obtaining the willing and informed participation of subjects may be too burdensome and may even prevent the pursuit of desirable research. Some states have enacted laws that specifically allow investigators within an institution to obtain medical records for research without seeking patient consent.⁸ These provisions, however, may conflict with the federal regulations that protect private information, and other state statutes provide greater protection than that mandated by federal law.⁹

In light of the variety of circumstances under which people provide tissue samples, these individuals are referred to as "sources" in the discussion that follows. (Annas et al¹ independently chose to use the term "sample source" in the Genetic Privacy Act they drafted [§3(n) and pp 49-51]. This act is a proposal for comprehensive federal legislation regarding genetic privacy.) This term, while impersonal, avoids some of the inaccurate connotations of other more commonly used designations. It is not appropriate, for example, to refer to people from whom samples are obtained as "donors" because the latter term implies an intent to make a gift or to relinquish control that may not apply to any particular individual. Similarly, the term "depositor," which has often been used in discussions of DNA banks, with its implication of an explicit desire to retain exclusive control, may be misleading.

In the discussion that follows, much weight is given to federal regulations regarding the protection of human subjects both because they are legally enforceable and because they are the embodiment of an attempt to strike a balance between the desire to increase knowledge and the protection of individual interests. This analysis reflects the workshop participants' understanding of these regulations based on the regulatory language and on documents published by the Office for

Protection From Research Risks. It must be acknowledged that there is room in some cases for differing interpretation, particularly since courts have rarely addressed these regulations. Areas in which the regulations do not provide complete guidance or where there are arguments for changing the regulations will be pointed out. Clearly, society's understanding of the ethical foundations of research is evolving so that continuing reexamination and amendment of legal rules may be warranted. Investigators should also seek guidance from their IRBs and institutional counsel regarding the laws of their own states.

ANONYMOUS SAMPLES FOR RESEARCH

According to federal regulations,¹⁰ the following is exempt from the requirements for protection of human subjects:

Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. . . .

Thus, use of anonymous samples for research is exempt as long as two stringent criteria are met. First, the samples must already be existing at the time the research begins. Second, as interpreted by workshop participants, identifiers must be irretrievably removed from the information or samples that will be studied. The workshop participants agreed that samples are anonymous if and only if it is impossible under any circumstances to identify the individual source. At present, in settings such as those involving large population groups, it may be possible to ensure anonymity while retaining some information about the individual source, such as ethnic origin, sex, age cohort, or limited clinical data, with the sample. In other settings, such as DNA samples obtained from a small group of individuals at risk for a specific disorder, retention of additional information may compromise anonymity. Samples are not anonymous if it is possible for any person to link the sample with its source. Even if the researcher cannot identify the source of tissue, the samples are not anonymous if some other individual or institution has this ability.

REMOVING IDENTIFIERS FROM EXISTING SAMPLES

There was much discussion about the appropriate use of already-existing samples that still retain identifiers at the time the research is designed. Fed-

eral regulations¹¹ currently permit investigators to take such samples without seeking consent, make them anonymous by removing identifiers, and then use them in research. Such an unidentified data set might fit within the strict language of the exemption or cease to qualify as a "human subject" under the regulations and so be exempt from review or might fit within the provisions for waiver.¹¹ Some of the workshop's participants argued that "anonymizing" samples without the sources' consent is ethically acceptable and that there is no possibility for stigmatization of the individual once identifiers are removed. Others argued, however, that anonymizing samples without consent is problematic because researchers had an opportunity to seek consent but did not exercise it. The propriety of removing identifiers from already-existing samples is an area that deserves further study.

Workshop members also raised but did not resolve questions about the use of tissue samples obtained in the future for anonymous research. There was consensus that, where use of anonymous tissue samples for specific research projects is anticipated at the time that the samples are obtained, sources' informed consent should be procured unless it can be waived in accordance with other provisions of the regulations.¹² Given the frequency with which genetic researchers use stored tissue samples, one could argue that consent for use for research should be obtained whenever a tissue sample is collected in the future. However, one could argue that obtaining consent at the time samples are collected in the course of clinical care may pose formidable logistical and practical problems, particularly when there is little chance that any one sample will be used for research.

Some have argued, moreover, that the regulations do not apply if samples are obtained in the course of clinical care because the regulations¹¹ state that a human subject is an individual "about whom an investigator . . . conducting research obtains data through intervention or interactions with the individual. . . . Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes." It is asserted, therefore, that individuals whose interventions are undertaken solely for clinical care are not human subjects under the definition even when the clinician is aware that research is contemplated. There are, however, two problems with this argument, one legal and one ethical. The legal problem is that since the definition is stated in the alternative, the individual is still a human subject if

the research involves "identifiable private information," no matter how obtained. Much of the information used for research is private as just noted. The ethical dilemma is that it is at best disingenuous and at worst deceptive for the clinician to obtain clinical samples knowing that they are likely to be used for research without mentioning this possibility to the patient. To the extent that the regulations permit samples obtained in this manner to be used for research without considering the need to obtain consent from the sources or to protect confidentiality, the regulations should be changed to require that these patients be given the same protections accorded to other human subjects.

Some members expressed concern that continuing to allow tissue samples to be collected without obtaining consent for anonymous research at the time of collection and then allowing investigators at a later time to use these samples after removing identifiers but without seeking consent could undermine public trust in research. The removal of identifiers without seeking consent also raises the ethical problem of not being able to offer sources the opportunity to be notified should effective interventions be developed to treat or prevent a particular genetic disease.

These and other problems led the workshop participants to agree that IRBs could usefully review research proposals to use currently anonymous samples and to make currently identifiable tissue samples anonymous without the sources' consent. Some participants urged that consideration be given to amending the regulations to require such reviews. In such reviews, IRBs should consider the criteria set forth in the "Specific Recommendations" section.

USE OF LINKABLE OR IDENTIFIED SAMPLES FOR RESEARCH

All research that proposes to use samples that are not now or will not be made anonymous requires more thorough review. A growing body of research involves the identification of mutations that have a known high risk of disease. Identification of these mutations, particularly where no interventions exist, carries psychological and social risks as well as the possibility of insurance discrimination. The risks involved with identifying these mutations must be distinguished from the risks of identifying genetic polymorphisms that involve common alleles that are neither necessary nor sufficient for the development of disease, many of which are risk factors only in combination with particular environmental exposures or lifestyle factors.

Potential Consequences for the Individual of Genetic Research on Identifiable Samples

Genetic information if revealed can have medical benefits as well as psychological and economic ramifications, both positive and negative, not only for the person from whom the sample was obtained but also for his or her relatives. Some may value having more knowledge about their own and their children's genetic makeup and possible predisposition to disease. Such individuals may appreciate the ability, where possible, to intervene to improve their own health and the health of their relatives and to make more informed reproductive choices.

Genetic research also can pose risks. Some participants may find that genetic information disrupts their lives, causing anxiety or other adverse psychological consequences, and may interfere with their relationships with family members, who may or may not desire the information. The disruption may be particularly severe when no effective treatments are available, as is true for many genetic disorders. Altering reproductive plans may not be desirable or even available to many individuals. Genetic information, if it becomes available to third parties, can raise barriers to individuals' access to employment and insurance.

Undertaking genetic research using identifiable samples without the consent of the sources can wrong them even if no direct harms that give rise to legally enforceable claims actually occur. Capron¹³ argues that, just as individuals are wronged if others enter their houses without consent, so too are they wronged if others obtain access to private information about them. In addition, undertaking research without consent fails to respect the preferences of some people who might have chosen not to provide the tissue samples at all or to put explicit limitations on their use.¹⁴ For example, some people may wish to limit the use of their samples to non-commercial entities. Others may wish to forbid the use of their samples to investigate certain disorders, particularly if the disorders are stigmatizing for a specific population group, as an alcoholism gene might be. In addition, retaining tissue samples or immortalizing cell lines may violate cultural or religious beliefs. Even if no harms or wrongs occur, people who provide tissue are less likely to receive many of the personal benefits that could result from participation if they are not aware that research is being performed. They could, however, benefit from the general advances in knowledge that might result from such research.

Initial Consequences for the Individual of Genetic Research Using Identifiable Samples

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Identified or Linkable Samples: Limited or No Informed Consent?

Regulations¹⁶ allow IRBs to approve research protocols in which subjects' consent is limited or not obtained. The following requirements

(1) involves no more than minimal risk to subjects; (2) the waiver or alteration does not adversely affect the rights of the subjects; (3) the research can be carried out without alteration; (4) whenever appropriate, subjects will be provided with sufficient information after par-

ticipating whether research on identifiable samples involves more than minimal risk and whether limited consent adversely affect the rights of the subjects, it is necessary to consider the magnitude of the psychosocial risk (which may be minimal in the case of genetic polymorphisms not expected to contribute to multiple diseases) and the likelihood that the information will be revealed to third parties. In a related decision, the Office for Protection From Research¹⁶ stated the following:

Research that generates information about an individual's personal health risks can cause anxiety and confusion, damage family relationships, and compromise the individual's ability and employment opportunities. Many genetic research projects pose psychosocial risks that can be significant to warrant careful IRB review. The fact that genetic information is limited to the collection of information and blood draws, and therefore, automatically classified as "minimal risk" studies qualified for IRB review.

Those who propose conveying genetic information to the source or to a third party generally pose more than minimal risk and so would require informed consent.

If disclosure is not planned, and if, in some, albeit often small, amount, genetic information may be made available to the sources or third parties, strict procedures to prevent the release of information to others, including a certificate of confidentiality from the assistant secretary for protection from compelled disclosure for personally identifiable information^{17,18} may make sense to designate a protocol as involving more than minimal risk. The issue is whether informed consent for the use of stored tissue samples is sufficient because obtaining it would be difficult. There has been little

litigation about the meaning of impracticability in the research setting, which means that the implications of this term have not been fully explored. In one case,¹⁹ however, the US Court of Appeals for the District of Columbia held that obtaining informed consent before the use of investigational drugs on combat soldiers during the Persian Gulf War was "impracticable," taking into account particularly urgent circumstances: a combat-zone setting, the safety of military personnel at that location, and the compelling need of the service members' mission."

This case, while clearly distinguishable from proposals to use stored tissue samples for genetic research, supports the position that it may be appropriate in unusual circumstances to forgo obtaining consent. In that case, the threat to the health of individuals was imminent, a situation that applies only to certain life-threatening genetic disorders for which there is clearly effective intervention and to extremely mutagenic environmental events that cause tremendous genetic damage. The concern that obtaining informed consent will lead some people to opt out and so affect generalizability of results should influence matters only where the need for the research results and the possibility and impact of bias are great. There is a legal and ethical presumption in favor of obtaining informed consent even though it means that much medical care is based on research that relies on biased samples because potential subjects could choose not to participate. Given that talking with people always entails some costs, consent cannot be waived on the simple assertion that seeking it would be tedious, burdensome or costly.²⁰ Rather, there must be proof that requiring consent would be so burdensome or expensive, as might be true were it necessary to contact the entire population, that the research could not go forward. The workshop participants agree that further discussion of the scope of impracticability is needed.

What Information Should Be Given to Sources to Enable Them to Decide Whether to Permit Their Samples to Be Used for Research?

The sources' consents will generally be required for research using linkable and identifiable samples. The investigator who proposes the research is responsible for ensuring that consent has been obtained from subjects. Obtaining permission from the institution or individual having custody of the samples without review of the initial consent will not suffice. It may, however, be appropriate for the individual's health care provider or a representative of the institution in which care was obtained to

approach the source to seek further consent. Even this approach is not without problems, because patients may feel obligated to participate in projects that their health care providers recommend.

Regardless of who actually makes contact with the person who provided the tissue, federal regulations require extensive disclosure about a wide array of topics.²¹ Sharing linkable or identifiable samples with researchers who are not involved in the source's care may pose particular risks to the individual. As required by federal regulations, such researchers should be bound to the limits of the original informed consent. Hence, the IRBs should require that copies of previous informed consent forms be examined to evaluate whether the new research conforms with or goes beyond the provisions of the original informed consent. Researchers who were not involved in the original sample collection should also show evidence that they are protected from having the results of their studies be subject to subpoena if the original investigator was so protected. These researchers should also consider obtaining certificates of confidentiality.

In addition to receiving the federally mandated disclosures, sources might want to hear about the possibility that research using their samples could lead to the development of commercially valuable products. Commentators have asked whether the source has any rightful claim to a share of the resulting profits. Others have expressed concern that offering sources a share of profits would be manipulative because the possibility that a profitable product will be developed from any particular research project is so low. The resolution of whether subjects are entitled to or should be permitted to share in commercial profits was beyond the scope of this workshop, but it should be noted as an unclear legal and ethical issue.

People may also wish to know that the researchers' interest in economic gain, academic or career advancement, or even fulfillment of intellectual curiosity may lead them to seek extra tissue. Patients and their families will often be willing to cooperate when apprised of the investigator's desires. Yet, cases such as *Moore v Regents of University of California*²² inform us that the possibility that a treating physician may collect more tissue than is necessary for diagnostic or therapeutic purposes should be disclosed, particularly if this increases the health risk to the patient. Similar concerns could arise were a researcher to obtain consent to obtain tissue from a subject for a particular project but then took extra tissue for another project of which the subject was unaware.

Under What Conditions Should Research Results Be Shared With Tissue Sources?

If tissue samples are used for genetic research, one must decide when, if ever, it is appropriate or even mandatory to recontact sources who provided the samples to provide them with test results. When research involves the use of anonymous samples, recontact is impossible, a point that should be made clear to people who agree to the use of their samples for anonymous research.

Research using linkable or identified samples poses different issues. Relying on cases that impose liability on physicians who fail to warn patients about newly discovered long-term effects of previously administered therapy, some commentators have argued that physicians who fail to recontact current and past patients when new diagnostic or therapeutic interventions become available may be subject to "look-back liability."^{23,24} While Annas et al^{1(pp142-165)} argue that concerns about such liability are unfounded, if this extension of liability were upheld, there might be a very small risk that investigators, particularly if they are also the sources' treating physicians, who fail to tell subjects about a mutation that predisposes them to colon cancer, for example, could be found liable if these individuals do not undergo periodic screening and later develop the disease. Where, however, the implications of a research finding are unclear or where there are no effective interventions, there could be no liability.

Some argue that respect for persons and the desirability of avoiding harm mandate some communication of results of genetic research.^{25,26} The regulations that govern the ability of IRBs to limit or waive the requirements of informed consent direct that consideration be given to providing subjects "with additional pertinent information after participation."¹⁵ However, others urge researchers to withhold some preliminary research results from subjects.¹⁶ Their concerns are that since early data are not interpretable, either there is nothing to convey or knowledge of preliminary findings will lead people inappropriately to take actions that may result in harm.

To avoid uncertainty about sharing research results and to limit possible liability, the best course is to inform people whose linkable or identified samples are going to be used in research about what types of information they can expect to have provided by the investigators. If the investigator wishes to recontact subjects, the circumstances under which this will and will not occur should be carefully delineated at the time consent for the use

of the samples is obtained. These subjects must also be offered the opportunity to refuse recontact.

USE OF SAMPLES OBTAINED FROM PEOPLE WHO HAVE SINCE DIED FOR GENETIC RESEARCH

Under the federal regulations governing the protection of human subjects, people are subjects only during their lifetime.¹¹ An argument can be made, therefore, that any use of samples obtained from individuals who have since died is not covered by the federal regulations. Yet since genetic research can reveal information that may pose psychosocial risks to living relatives, it may be appropriate, particularly in circumstances where the risk is high, to allow relatives to veto the use of their relative's linkable or identified samples unless the person who was the source of the sample had previously explicitly consented to the research. The absence of risks to living people, by contrast, may justify the use for genetic research of anonymous samples obtained from those who subsequently died. The investigator should, however, honor the wishes of people who did not want their samples to be used even for anonymous research. In any event, it is inappropriate and usually illegal to obtain tissue samples after a person's death without consent either from the person before death or from relatives.

USE OF TISSUE SAMPLES FROM CHILDREN FOR GENETIC RESEARCH

The question of the permissible scope of genetic testing of children raises issues about the appropriate scope of parental authority to make decisions regarding their children, physicians' and the state's power to limit parental decision making, and the obligation to listen to children's voices about their own care. The appropriate balance among these forces has recently been the subject of intense debate that reaches beyond the scope of this document.²⁷⁻²⁹ Even so, federal regulations governing research in children, while making clear that such projects require additional caution, allow at least some areas of consensus regarding the use of tissue samples from children for research.

As is true for adults, research using linkable or identified tissue samples from children, particularly to search for mutations that cause specific diseases, usually poses greater than minimal risk. As a result, permission to use a sample must be sought from a parent of the source, and assent, if appropriate, must be sought from the child.³⁰ Strictly speaking, informed consent applies only to decisions

made by competent individuals regarding their own care and so usually does not apply to decision making regarding children. There is growing consensus that the parents' role is one of giving permission and that children as they grow older are entitled to decide whether they wish to proceed with therapy or research.²¹

All genetic research involving children should also be structured in a way that allows the children to retain as many choices and opportunities as possible once they reach adulthood. As a result, if a child's samples are used for research, care should be taken to ensure that the results not be entered into the child's medical record unless relevant to the child's immediate medical care to minimize the risk of inadvertent disclosure to the child or to third parties.

'OPTING IN' VS 'OPTING OUT' OF THE USE OF TISSUE SAMPLES FOR GENETIC RESEARCH

Arguing that people who provide tissue samples should be asked for permission to use their samples does not mean that written informed consent is required in all circumstances. There should be a strong presumption in favor of doing research only on samples of individuals who "opt in" to participation by signing a document. In some circumstances, however, it may be appropriate for such research to proceed as long as subjects do not "opt out" of research after sufficient efforts have been made to ensure that they are adequately informed. An instance in which some in the workshop reasoned that this might be an appropriate course is in proposals to remove identifiers from currently identifiable stored tissue samples that were obtained years ago from people who are still alive.

PUBLIC HEALTH INVESTIGATIONS

Investigations of disease clusters may present different considerations from those involved in research. Specifically, timely determination of the cause of disease in a community may not be viewed as research but rather is needed to determine what, if any, intervention is warranted to avert the occurrence of new cases. To this end, investigators may wish to examine an array of potential causes, from infectious, environmental, nutritional, and occupational factors to genetic susceptibility, and they may search for gene-environment interactions as the cause of disease. The interventions performed in the name of public health can vary depending on the cause of the disorder. Detecting a primarily infectious cause may lead to a dramatically different response compared with finding that the incidence of disease depends heavily

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on genetic susceptibility. The extent to which the public through its agents can undertake these investigations and act to limit the incidence of disease or disability without seeking the consent from patients or subjects traditionally sought in medical care or research raises questions beyond the scope of this discussion. At a minimum, however, the state's power to act is clearest in cases of medical or public health emergency and wanes as the health problems pose less immediate threat to individuals and the community.

SPECIFIC RECOMMENDATIONS

The major observation of this workshop is that current federal regulations require IRB review and often the sources' consent for many proposals to use stored tissue samples for genetic research. The specific implications of the federal regulations for genetic research are described herein.

Use of Biologic Samples That Have Already Been Collected

Determining How to Proceed When Samples Are Not Anonymous at the Time That the Research Is Proposed.—Informed consent that complies with the requirements defined in the "Collection of Tissue Samples in the Future" section is required if the investigator wishes to use identifiable or linked samples. Before requiring that a source be recontacted to obtain consent, the investigator and the IRB should determine whether the person who provided the sample previously agreed to the use of the sample for genetic research. Even in the absence of specific language about DNA testing, it may be appropriate to infer consent if the source wished for the sample to be used to determine why his or her family had a particular inherited disorder. By contrast, rarely does the language in typical operative and hospital admission consent forms provide an adequate basis for inferring consent to genetic research. If the IRB determines that the proposed research was agreed to by the source at the time the sample was obtained, then there is no need for further consent, although the IRB may choose to require that the investigator inform the sources, if still alive, about the new project and provide general news about the results.

Limitation or waiver of consent may be appropriate in some circumstances under the regulations or in emergency public health situations. The burden is on the investigator to justify seeking an exemption from obtaining full consent by meeting all the following regulatory requirements¹⁵:

(1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights

and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation. . . .

In deciding how to assess protocols that propose to make existing identifiable samples anonymous for use in research, IRBs should consider the following factors: (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.

Is There Any Role for IRB Review of Protocols That Would Use Samples That Have Already Been Stripped of Identifiers?—Such protocols are exempt from review under current regulations. The workshop attendees agreed that IRBs nonetheless could usefully review such protocols to determine whether they are scientifically sound (particularly for protocols that have not already been subjected to peer review), whether they propose to address a significant problem, and whether the desired information could be obtained in a protocol that allows individuals to consent.

Collection of Samples in the Future

People should have the opportunity to decide whether their samples will be used for research. This option should be presented when samples are collected for whatever reason if it is likely that the samples will also be used for research. In addition, the possibility of future research should generally be discussed whenever tissue samples are collected for any research project.

If people agree to such use, they should then be offered the following options:

1. Whether they are willing to have their samples used in identifiable or linked research. To make this complex decision, potential subjects must be informed about (a) the risks and benefits of participation; (b) the extent to which confidentiality realistically will be maintained. Investigators are strongly encouraged to seek cer-

tificates of confidentiality; (c) under what circumstances, if any, they will be recontacted. If recontact may occur, subjects must be offered the opportunity to refuse to participate. Even if specific information will not be made available, researchers could offer to send a periodic newsletter to participants so that they can be aware of new findings and can seek them through their health care provider if they are interested. The circumstances under which the researcher will decline to provide preliminary results either in individual contacts or in the newsletters should also be defined; and (d) their ability to withdraw from the project in the future. In general, a decision to withdraw should allow the individual to stop any further personal involvement and to withdraw any samples or data that contain identifiers from use in research that occurs after the date of withdrawal.

Because of the complexity of the issues that individuals must consider in deciding whether to participate in such research, the workshop participants believe that it is not desirable to ask sources to sign statements in which they agree to the use of their identifiable samples for research without being informed about the scope and potential consequences of the projects.

2. Whether they wish or are willing to have their samples stripped of identifiers for use in research. Individuals should be told that when their samples are used anonymously, they cannot be given specific information about findings related to their samples.

Whether people permit researchers to use identifiable or anonymous samples, they should be informed of the extent to which the researcher may be motivated by interests other than those of the source. People should be told whether they will share in the profits of any commercial products that might be developed based on findings from the research.

In addition, many at the workshop urged that people who provide tissue samples, particularly for use in identified or linkable research, should also be given the following choices:

1. Whether they are willing to have their samples shared with other investigators either inside or outside the institution in which they are collected. Individuals may wish to permit their samples to be used only by investigators at academic institutions and not by those involved with commercial enterprises, although the distinctions between these two groups are increasingly difficult to define. In any event, samples should be shared with investigators who were not involved in the research project to which the subjects agreed only after identifiers have been removed.

2. Whether they wish their samples to be used only to study certain disorders. Some individuals may wish to limit the use of their samples to specific diseases in which they are interested, such as breast cancer or cystic fibrosis. Others may wish to specify that their samples not be used to study certain classes of disorders, such as behavior-related diseases, disorders that are currently untreatable, diseases that are particularly stigmatizing to members of a group, or those for which prenatal diagnosis is the primary option.

Suggestions and Questions for the Future

The group recommends the enactment of more general legislation to ensure that no person or institution be able to obtain access, even by court order or subpoena, to either the samples used in research or the specific results of research performed on such samples. Although protection may already be provided by certificates of confidentiality, sources are entitled to this higher level of protection in exchange for allowing their samples to be used for research.

The group also urges that legislation be enacted to protect individuals who participate in research from loss of their health insurance or other adverse socioeconomic consequences. While creating such protection will undoubtedly be complex, providing this sort of protection not only will justly reward those who chose to contribute to the community by participating as subjects but also will promote research by allowing some individuals to participate who otherwise would have chosen not to out of fear.

Several issues emerged in the course

of the workshop and the revising of this document that are still unresolved. One is the degree of deference that should be given to individuals' desires not to have samples of their tissues used for specific types of genetic research. Another is whether there is any need to seek consent from people who provided currently identifiable tissue samples for proposals that plan to remove identifiers. Still another is whether research using anonymous samples should be disfavored if the information can be obtained in a project that obtains individual consent. The attendees agreed that greater consideration should be given to examining the limits of impracticability.

The workshop participants recognize that while they sought in this document to provide guidance for resolving many issues regarding the use of stored tissue samples for genetic research, they raised many questions that merit broad-based discussion. Efforts to determine how best to pursue genetic research depend in part on achieving an accurate understanding of the personal and social benefits and risks that may accompany genetic research and of the costs and benefits of seeking consent. Society at large must decide how it wishes to weigh the value of respecting persons with the desirability of obtaining socially useful knowledge in a timely manner and of individuals' participating in such research, particularly if the personal risks to them are small. The workshop participants acknowledge that the costs of seeking consent may preclude some projects designed to study linkable samples that involve greater than minimal risk. They also acknowledge that the federal regulations for protection of human subjects

already address this issue. Deciding how to proceed with research is not a static process, but rather requires continuing reexamination over time.

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