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Informed Consent in Genetic Research

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History demonstrates that, without adequate informed consent, research participants' rights may be violated and their confidence in research as an enterprise undermined. If participants lose confidence in research, they may hesitate to participate in future research protocols. Without human participants to donate biological samples and participate in protocols, research will be difficult, if not impossible to conduct. Thus, appropriate informed consent protects both research participants and the enterprise of research itself. Informed consent principles in genetics not only help ensure the appropriateness of specific research protocols, but they also help support the continuation of all types of research on human participants. Most research involving human participants raises some issues fundamental to the informed consent process, such as whether potential participants truly understand the consequences of their participation in a study, and in which circumstances a person is competent to give consent. Advances in genetics are raising a new set of informed consent issues. The risks that may be involved in genetic research extend far beyond the standard considerations of immediate potential harm to study participants. Genetic information carries with it the possibility of uncovering a future propensity for a given illness. The disclosure of genetic information may lead to problems in obtaining health insurance, employment and/or housing discrimination, and to social and personal problems not only for participants, but also for their family members.

Key words: *DNA; ethics, medical; informed consent; genetics; research; genetic screening*

Informed consent principles in genetics (1) not only help ensure the appropriateness of specific research protocols, but they also support the continuation of all types of research on human participants. History demonstrates that, without adequate informed consent, participants' rights may be violated and their confidence in research as an enterprise may be undermined. If participants lose confidence in research, they may hesitate to participate in future research protocols. Without human participants to donate biological samples and to participate in protocols, research will be difficult, if not impossible to conduct. Thus, appropriate informed consent protects both research participants and the enterprise of research itself.

Most research involving human participants raises some issues fundamental to the informed consent process, such as whether potential participants truly understand the consequences of their participation in a study, and in which circumstances a person is competent to give consent. Advances in genetics are raising a new set of informed consent issues. The risks that may be involved in genetic research extend far beyond the standard considerations of immediate potential harm to study participants. Genetic information carries with it the possibility of uncovering a future propensity for a given illness. The disclosure of genetic information may lead to problems obtaining health insurance, employment and/or housing discrimination, and to social and personal problems not only for participants, but also for their family members. As a result, some genetic testing and research may require professional counseling to ensure that the ramifications of participation in genetic research are properly disclosed and comprehended by each research participant (2,3).

Many organizations have initiated recommendations on use of archival material in genetic research (4,5). The complexities of genetic research have been elucidated in a number of recent statements and reports (6-13). To understand the current ethical and regulatory climate, a brief look back at the history of guidelines governing informed consent is invaluable.

Brief History of Informed Consent

Over the past four decades, informed consent in medical research has become an increasingly important issue as attitudes toward patients' and participants' rights and roles have evolved. Before the 1940s, physicians' and researchers' official guidance stemmed primarily from the tenants of the Hippocratic Oath. One version of the Oath, the first set of Western writings about medical professional conduct, highlighted a number of problems with truth telling by the physician. It advised of the wisdom of "concealing most things from the patient while you are attending to him or her... turning his or her atten-

tion away from what is being done to him or her", and "...revealing nothing of the patient's future or present condition" (14,15). The premise was that judgment of medical professionals was superior to that of the less knowledgeable patients and subjects. Medical decision-making was characterized as a burden, not a right.

In 1945 and 1946, that characterization changed. Largely in response to the Holocaust atrocities committed in the name of genocide and medical research, the Nuremberg Code was enacted (16). The first principle of the Code required informed consent. The informed consent principle gave little credence to the notion that doctor knows best. Instead, it commanded researchers not only to inform, but also to seek consent from potential research participants:

"The voluntary consent of the human subject is absolutely essential. This means that "the person involved should have the legal capacity to give consent... should be so situated as to be able to exercise free power of choice... [and] should have sufficient knowledge and comprehension of the subject matter involved as to enable him (or her) to make an understanding and enlightened decision" (15,17).

At the time that the Code was enacted, it did not receive full credence in the United States. In fact, at that time, vulnerable populations in the United States, such as the mentally disabled and prisoners, were being used as research participants (15).

In 1962, United States federal government enacted its first piece of legislation addressing informed consent – "The Drug Amendments of 1962" (P.L. 87-781), section 505 (I) of the Food, Drug, and Cosmetic Act (15,18). These Amendments required researchers testing investigational new drugs to obtain their subjects' "consent or that of their representatives, except where [the researchers] deem it not feasible or in their professional judgment, contrary to the best interests of such human beings" (15,19). The Amendment addressed some pressing informed consent issues but with no external or policing mechanisms, left the adherence to informed consent guidelines largely in the hands of individual researchers.

In 1964, the international medical research community created its own code, adopted by the World Medical Association as the Helsinki Code (20). This self-imposed set of rules allowed researchers to have considerable latitude in the area of informed consent for therapeutic research. Non-therapeutic research required informed consent from the participant or that of a proxy decision-maker. Research combined with professional care was allowable without informed consent if, in the physician's judgment, "it offer[ed] hope of saving life, re-establishing health, or alleviating suffering", and if consent was not "consistent with patient psychology" (15,21). The so-called "therapeutic loophole" was viewed by many as a serious flaw in the Code.

In 1966, the United States Surgeon General responded to criticisms of U.S. informed consent policies by publishing "Clinical Investigations Using Human Subjects" (14), a policy directive requiring institutional review of Public Health Service-supported protocols involving human participants. According to this policy, each potential protocol had to be reviewed by an institutional committee charged with ensuring the rights and welfare of the research participants, checking the appropriateness of the informed consent methodology, and weighing the risks and benefits of the research (14,15). The Surgeon General's policy, though addressing the self-regulation issue, failed to adequately define key terms, such as "rights and welfare of potential subjects", "informed consent", and "risks and potential benefits". The lack of definitions led to confusion and arbitrary application of the policy (14,15).

In 1971, the Department of Health, Education, and Welfare (DHEW) (now the Department of Health and Human Services) defined many of the missing terms in its "Institutional Guide to DHEW Policy and Protection of Human Subjects" (22). The Guide improved upon the Surgeon General's policy by listing required elements of informed consent and requiring continuing review of ongoing research projects (15,23). Still, some issues remained unresolved, such as institutional review committee composition, research-related injury compensation, distributive justice in the participant selection process, and the achievement of adequate informed consent (14,15).

As the shortcomings of the 1971 policy were coming to light, in 1972 the public learned about the story of the Tuskeegee Study, a Public Health Service-funded project (24). For 40 years, 19 years past the discovery of penicillin, researchers withheld treatment for syphilis from hundreds of black men in Alabama to study the continuing effects of the disease. In response to criticisms of the 1971 policy and the Tuskeegee Study, the Director of the NIH created a Public Health Service Committee to examine issues related to the regulation of human research (15). The Public Health Service Committee recommendations, issued in 1973, were implemented in DHEW regulations published in 1974. Save a few narrow exceptions, they applied to all DHEW supported and/or conducted grants and contracts that involved human participants (25). In 1991, the 1974 regulations were revised slightly and adopted by a myriad of government agencies as the "Common Rule". The Common Rule now applies to the Office of Science and Technology Policy, Department of Agriculture, Department of Energy, National Aeronautics and Space Administration, Department of Defense, Consumer Product Safety Commission, International Development Cooperation Agency (Agency for International Development), Department of Housing and Urban Development, Department of Justice, Department of Defense, Department of Education, Department of Veterans Affairs, Environmental Protection Agency, National Science Foundation, Department of Transportation, and Department of Health and Human Services (Office of the Secretary and Food and Drug Administration) (15).

Current and Emerging Rules and Regulations

When conducting research on human participants, a researcher must abide by international, na-

tional, state, and institutional rules and regulations. One seemingly simple threshold question is whether human participants are involved. According to the National Institutes of Health, legal obligations to protect human participants apply to research that uses *bodily materials* (e.g., cells, blood, urine, tissues, etc); *residual diagnostic specimens,* including those "obtained for routine patient care that would have been discarded if not used for research"; and *private information,* "such as medical information that can be readily identified with individuals, even if the information was not specifically collected for the study in question" (26). In short, regulations governing research on human participants may attach to projects that do not directly involve human beings (27).

Common Rule

Most research involving human participants in the United States is governed by the "Common Rule" (28). According to the Common Rule, Institutional Review Boards, clinical investigators, and research sponsors share the responsibility for ensuring adequate informed consent. The Common Rule outlines the following informed consent requirements:

1) Informed consent must be obtained from the subject (or the subject's legally authorized representative) before a subject can be involved in research.

2) The investigator must seek consent under circumstances that give a subject sufficient opportunity to consider whether to participate and that minimize possible coercion or undue influence. Circumstances surrounding the consent process (timing, setting, who obtains the informed consent and other details) are important to the subject's ability to comprehend the information provided.

3) The information given to subjects must be understandable to them. Technical and medical terminology should be avoided or must be explained, and non-English speaking subjects must have the information presented in a language that they understand.

4) The informed consent document may not include exculpatory language through which the subject is made to waive or appear to waive and legal rights or releases of appears to release the investigator, the sponsor, the institution, or their agents from liability for negligence.

The Common Rule also requires that informed consent contain the following elements for all non-exempt, federally funded research conducted on human participants in the United States:

1) a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

2) a description of any foreseeable risks or discomforts to the subject;

3) a description of and benefits to the subject or to others which may reasonably be expected from the research;

4) a disclosure of appropriate alternative procedures of treatment, if any, that might be advantageous to the subject;

5) a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

6) for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether and medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

7) an explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and (when appropriate) whom to contact in the event of a research-related injury to the subject; and

8) a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Further information about informed consent and Institutional Review Board requirements is available in the publication "Protecting Human Research Subjects" from the NIH Office for Protection from Research Risks (OPRR) 1993 Institutional Review Board Guidebook (29).

Recent Regulatory Trends

Regulations that govern clinical trials and genetics are evolving with new developments, issues, and demands. Presently, several key policies and pieces of legislation, court cases, and rules are being considered, which might have implications for informed consent and genetic research. On June 5, 2000, the National Institutes of Health (NIH) released new rules requiring education in the protection of human research participants (30). This rule required that all principal investigators and Institutional Review Board members receive training to conduct human participant research. It took effect on October 1, 2000, but was subsequently repealed for procedural reasons. The rule is expected to be reissued in keeping with proper protocol. This means that all Institutional Review Board members and principal investigators associated with research on human participants and grant money from the NIH should consider enrolling in a course that yields a certificate for training on the protection of human research participants (31).

On December 28, 2000, the Department of Health and Human Services published a final rule, the Privacy Rule, adopting standards for the privacy of individually identifiable health information. The Privacy Rule is the second in a series of rules mandated by sections 261-264 of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), Public Law 104-191. Subpart E of the Privacy Rule "establishes standards which entities covered by the statute – health plans, health care clearinghouses, and certain health care providers – are required to comply with to protect the privacy of certain individually identifiable health information ("protected health in-

formation"). The standards are requirements relating to the uses and disclosures of protected health information, the rights of individuals with respect to their protected health information, and the procedures for exercising those rights" (32).

The Privacy Rule restricts the transfer of medical information without the specific consent of the participant. Therefore, informed consent documents should contain recontact provisions to help facilitate follow-up research.

On January 18, 2001, The Food and Drug Administration (FDA) issued a proposed new regulation entitled "Availability for Public Disclosure and Submission to FDA for Public Disclosure of Certain Data and Information related to Human Gene Therapy and Xenotransplantation" (33). As proposed, this rule addresses the confidentiality and would make certain data related to human gene therapy available to the public. The regulation was proposed because human gene therapy has "the potential for unique public health risks and modification of the genome" (33). Public commentary regarding this proposal is being solicited through April 2001, after which time a permanent regulation may be issued. If enacted, informed consent may need to account for the possibility of mandated public disclosures of information.

On February 19, 2001, the Equal Employment Opportunity Commission filed a Petition for a Preliminary Injunction against Burlington Northern Santa Fe Railroad to end genetic testing of employees who have filed claims for work-related injuries based on carpal tunnel syndrome (34). This suit seeks to prevent employers denying work-related injury claims based upon genetic information regarding a predisposition to a particular condition. The success of the Equal Employment Opportunity Commission action may in turn help to assuage some public fears relating to the potential consequences of genetic testing, and thus help to facilitate genetic research.

Planning Ahead

The pursuit of advances in genetic technologies and research has the potential to raise novel ethical and legal issues. The collection of appropriate informed consent at the beginning of research projects can eschew, lessen, or completely eliminate these and other potential problems. Some foresight combined with a general awareness of the probable and potential problems that can arise over the course of genetic research studies supports the smooth continuation of genetic research protocols. To that end, this section highlights the common problem areas of genetic research and their informed consent cures.

Tiered Consent and Security

In many instances, genetic research can be easily conducted through the use of previously collected tissue samples or information. Tiered informed consent and security measures can help facilitate the ethical re-use of biological materials and associated information.

One example of tiered informed consent is contained a 1997 National Heart Lung and Blood Institute (NHLBI) Special Emphasis Panel (SEP) Report on Opportunities and Obstacles to Genetic Research in NHLBI Clinical Studies (35). The Report suggests that researchers submitting proposals to NHLBI obtain "layered" or "multilevel" consent, as follows:

"For prospective studies, a layered or multilevel consent is recommended. The first level of consent should be for the current study, including genetic aspects, and should cover use of the specimen by the investigator and collaborators, recontact of subjects, and storage and reuse all to accomplish the goals of the study by the original investigators and collaborators. If identifiers will not be needed, consent for collecting the specimen anonymously, or for anonymizing it, should be obtained.

The second level of consent should cover use, recontact, and storage for goals broadly related to the area of the original study. If the subject refuses retention of the specimen with identifiers for these purposes, his/her consent for anonymizing the specimen should be sought. If the subject declines, the specimen should be destroyed at the conclusion of the current study.

The third level should be for use, recontact, and storage for goals unrelated to the area of the original study. The same choices and actions should be followed as for the second level (35)."

Tissue Storage and Shared Biomaterials

Collection of samples from repositories raises its own set of issues relating to informed consent in genetic research (36). Though researchers obtaining samples from repositories have no direct contact with donors and thus cannot obtain informed consent directly, they may still take some measures to ensure that informed consent was sought during the collection process. Repositories are moving toward documenting depositors' assurances that donors' informed consents were obtained during sampling. To help protect their research, those seeking to obtain biological samples for research may request the pledge of the repository that informed consent assurance was documented. Users should also be informed about restrictions that may have been placed on the biological samples, particularly those necessary to respect the scope of informed consent obtained from the donors.

Repositories have collected samples before many modern informed consent concerns arose, so informed consent may not have been sought and may not be possible to achieve due to the anonymity of the individual donors. However, in cases in which the donors are anonymous, research results have little potential to harm the donors. Though policy is changing over time, in cases in which no record exists of the informed consent of donors of anonymous samples, custom presently suggests that research may be conducted without assurances of informed consent.

Researchers considering storing biological materials and/or the information derived from them should note that several approaches to safeguarding genetic information currently exist. One mechanism is simply *not to store* the information and/or tissue samples. This approach may heighten individual privacy pro-

tection, but may also inhibit future research and/or medical care because of the time and resources required to re-collect the information. A non-storage system may interfere with follow-up medical care or future research.

At the other end of the spectrum from the non-stored information lie *personally identifiable data*. As the name suggests, personally identifiable data could enable a person without prior knowledge of the data or their collection to deduce the identity of data-participants. This type of information storage for genetic material stands largely at odds with American society, which "traditionally places a high value on privacy, personal autonomy, and free will in decision-making" (37).

Another data-storage approach is the *anonymization* of the sample or information. Data are said to be truly anonymized if "a person without prior knowledge of the data or their collection can(not), from the data and any other available information (such as postal charts, or a casually held key-code, or a list of the people recruited to the study), deduce the personal identity of data-subjects" (38). Data may be anonymized by not collecting or completely removing identifiers, by aggregating data into groups and ranges and not reporting individuals' identities, or by "micro-aggregating" the data into pseudo-cases representative of the real population (38,39).

Though much useful health research is conducted on anonymized data (38), the following are reasons why maintaining personal identifiability may be important:

a) To allow technical validation of reports, such as to confirm correspondence of various data with the data subjects, or even to verify the very existence of the identity of the subjects, in order to prevent scientific errors or fraud;

b) To avoid duplicate records or redundant cases, such as to be certain that two case reports are independent and not just the same case recorded in two files;

c) To facilitate internal scientific data-quality control, such as enabling working-back to original records and ancillary data;

d) To allow case follow-up if more evidence or confirmation are needed;

e) To check data-subject consent on records, or to examine Institutional Review Board stipulations or opinions in a case;

f) To allow tracking of consequences after some research intervention, to be able later, if necessary, to notify the patient or physician and recommend reexamination or other measures in-between research and health care; and

g) To ensure accurate correspondence in linking data on data-subjects, or groups, or specimens, among different files or databases, perhaps over a long period, even over decades, and possibly to follow-on to descendants (38).

An intermediate form of data storage that is neither readily personally identifiable nor truly anonymized, is *key coded data*. Data are key coded if their personal identifiers have been removed and secreted, but are still potentially traceable via a matching, separately held code (38). Properly executed, key coded data can provide general anonymity for research participants without triggering any of the above risks of permanently anonymizing data.

Several mechanisms may be helpful in key-coding data successfully. The NHLBI recommends holding the identifiers close to the point of collection (38). The U.S. National Institute of Alcohol Abuse and Alcoholism assigns a key-coded pseudonym to all participants and has the key securely held by an independent third party (38). The U.S. National Institute for Child Health and Human Development (NICHD) requires researchers wishing to perform secondary studies on data originally collected by other investigators under an NICHD grant to pay a fee. The original researchers then use the fee money to key-code the identifiers and to take other protective steps before sharing the data (38). Whatever specific measures are taken, effective key-coding requires identifiers to be locked up separately from data, linking codes to be safeguarded either by a reliable person or by a trusted intermediary, and, the process of linking back to the original data-participant to be carefully managed (38).

Cross-Cultural Studies and Document Readability

Cultural differences between researchers and donor populations can interfere with the collection of meaningful informed consent. Most obviously, in cases in which researchers and donors do not share a common language, informed consent documents and protocols should be constructed to meaningfully transmit information to the donor populations. The same may be true for illiterate individuals, low-literacy populations, and non-native speakers. In all populations, researchers should bear in mind that the majority of donors will not be scientists by trade, and thus may not understand technical language or terms of art. For that reason, informed consent documents and protocols should be drafted with the donor's perspective in mind and with the goal of educating each prospective donor. Some useful evaluative tools are available via the Internet to help assess the reading level of a document (40-42).

Different cultures also have their own customs and expectations, which researchers should take care to respect throughout the course of the research. The following suggestions for ensuring cultural respect are based, in part, on recommendations from the North American Regional Committee of the Human Genome Diversity Project (43):

1) *Preliminary Cultural Research* via anthropologists or others knowledgeable about the population should be conducted. This may reveal important information, such as the fact that some cultures associate the collection of hair or fingernail clippings with witchcraft, or that others have strict prohibitions on the donation of blood. Appropriate preliminary cultural research will facilitate the collection of adequate informed consent and will prevent the planning of culturally unfeasible protocols.

2) *Permission of Donor Populations' Government and/or Community Leaders* may be necessary and will probably help researchers to avoid initiating culturally or politically untenable research projects. Respect for donors' cultures and pragmatic concerns dictate that consent of the population, through its culturally appropriate authorities where such authority exists, should be obtained before sampling begins.

3) *Individual Donors' Consent* must also be obtained in accordance with the guidelines listed above. Researchers should be cognizant of the possibility that certain subgroups may have subordinated cultural positions, such that consent from their members may be suspect. "Such groups may include, in some cultures, low class or caste individuals, prisoners, particular minority groups, or women, among others... Securing the collective permission of the subordinated group may provide some extra assurances."

Through a combination of conducting preliminary research, obtaining permission from the government and/or community leaders, and seeking individual donors' informed consent, researchers can create a meaningful informed consent process and ethically sound research. In this way, researchers can help to generate exceptional ethical studies that benefit humankind.

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