7.3.7 Safeguards in the Use of DNA Databanks

DNA databanks facilitate population-based research into the genetic components of complex diseases. These databanks derive their power from integrating genetic and clinical data, as well as data on health, lifestyle, and environment about large samples of individuals. However, the use of DNA databanks in genomic research also raises the possibility of harm to individual participants, their families, and even populations.

Breach of confidentiality of information contained in DNA databanks may result in discrimination or stigmatization and may carry implications for important personal choices, such as reproductive choices. Human participants who contribute to research involving DNA databanks have a right to be informed about the nature and scope of the research and to make decisions about how their information may be used.

In addition to having adequate training to be able to discuss genomic research and related ethical issues with patients or prospective research participants, physician-researchers who are involved in genomic research using DNA databanks should:

Research involving individuals

(a) Obtain informed consent from participants in genomic research, in keeping with ethics guidance. In addition, physicians should put special emphasis in the consent process on disclosing:

    (i) the specific privacy standards to which the study will adhere, including whether the information or biological sample will be encrypted and remain identifiable to the researcher or will be completely de-identified;

    (ii) whether participants whose data will be encrypted rather than de-identified can expect to be contacted in the future about findings or be invited to participate in additional research, either related to the current protocol or for other research purposes;

    (iii) whether researchers or participants stand to gain financially from research findings, and any conflicts of interest researchers may have in regard to the research, in keeping with ethics guidance;

    (iv) when, if ever, archived information or samples will be discarded;

    (v) participants' freedom to refuse use of their biological materials without penalty.

Research involving identifiable communities

(b) When research is to be conducted within a defined subset of the general population, physicians should:

    (i) consult with the community in advance to design a study that is sensitive to community concerns and that will minimize harm for the community, as well as for individual participants. Physicians should not carry out a study when there is substantial opposition to the research within the community of interest;

(ii) protect confidentiality by encrypting any demographic or identifying information that is not required for the study's purpose.

AMA Principles of Medical Ethics: I,IV,V,VI

Background report(s):

CEJA Report 3-A-16 Modernized *Code of Medical Ethics*

CEJA Report 4-I-01 The use of DNA databanks in genomic research—the imperative of informed consent

7.3.7 Safeguards in the Use of DNA Databanks

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AMA Principles of Medical Ethics: I,IV,V,VI

members to warn them of their at-risk status. The latter model is more burdensome for the physician, who must try to find family members and breach patient confidentiality.

CONCLUSION

It is crucial that individuals who contemplate undergoing genetic testing receive adequate education and counseling from a qualified healthcare professional as part of the process of informed consent. Before deciding to have the test, individuals should understand the consequences of the information, both for themselves and for their biological relatives. Before they can communicate any of these details to patients accurately and thoroughly, many physicians will need to become more educated about the role of genetics in medicine and specific conditions for which they offer testing.

Patients must be informed in advance which information will be disclosed, and to whom. The biological relatives, whom physicians need expend only reasonable efforts to find, should receive adequate education and counseling, before being given the option to learn results. Only very exceptional circumstances would justify disclosure of information against a patient's will. Specifically, the information revealed by genetic testing would have to be such that it places the identifiable biological relatives at imminent, serious danger that could be averted if the relatives obtained the information.

RECOMMENDATIONS

The Council recommends that the following be adopted and the remainder of the report be filed:

1. Physicians have a professional duty to protect the confidentiality of their patients' genetic information.

2. Physicians who order genetic tests should have adequate knowledge to impart accurate information to patients. In the absence of adequate expertise in pre-test and post-test counseling, the primary physician should refer the patient to an appropriate specialist.

3. Pre-test counseling should include implications of genetic information for patients' biological relatives. At the time when patients are considering undergoing genetic testing, physicians should discuss with them the importance of informing those family members.

4. Physicians should inform patients what exceptional circumstances would ethically compel the physician to attempt to contact potentially affected biological relatives, even without the patient's approval. The physician should apply the most stringent standard of disclosure--immediate and preventable harm to identifiable biological relatives--in determining whether it is ethically justifiable to breach confidentiality. It should be noted that currently these guidelines establish a standard for situations that are unlikely to occur in practice.

5. Physicians should support the strengthening of genetic education at all levels of medical education.

(References pertaining to Report 3 of the Council on Ethical and Judicial Affairs are available from the Division of Ethics Standards.)

4. THE USE OF DNA DATABANKS IN GENOMIC RESEARCH: THE IMPERATIVE OF INFORMED CONSENT

HOUSE ACTION: RECOMMENDATION ADOPTED AND REMAINDER OF REPORT FILED

INTRODUCTION

Genomic research, which uses DNA to identify the gene(s) responsible for complex diseases, relies upon large DNA databases to facilitate population-based research. These databases derive their power from integrating different kinds of information about large samples of individuals--genetic and clinical data, data on health, lifestyle, and environment. Using statistical analysis, the databases can be used to analyze correlations that may enable new therapeutic developments.

The use of DNA databanks in genomic research brings new challenges related to the scope of research as well as to the nature and use of the samples and information archived in such databases. This report identifies these issues and considers their relation to the current standard of informed consent in human research.

NEW CHALLENGES

Nature of DNA Material

At the outset, several characteristics that are unique to DNA material (DNA samples or information derived from them) should be acknowledged. For instance, DNA material may include information about patients and their immediate biological family members that is entirely unknown to any of them--either because it has not been analyzed or because, in the absence of more advanced technology, it is not yet decipherable. Another characteristic specific to genetic information includes the fact that it can forecast disease long before a person shows any symptom. Also, given the stability of the DNA molecule, the nucleotide sequence in samples is usually immutable. More importantly with regard to research, once collected and stored, a DNA sample can be duplicated almost indefinitely by polymerase chain reaction (PCR) and used in the future to answer questions that were not contemplated at the time the sample was obtained. Once a researcher has a subject's DNA material, the stored sample or the data derived from it can be used for any number of future research protocols.

These various features may raise special risks for individual research subjects whose DNA material is stored in databanks. The harms that could result to subjects from these risks are distinct from the physical harms that generally are associated with clinical research trials, such as the harm caused by the side effect of an experimental drug. Foreseeable harms from genomic research include insurance, employment, and education discrimination, social stigmatization, improper attempts to influence reproduction decisions, and distress caused by information regarding the statistical possibility of disease. These may be a source of distress not only for research subjects, but for also their family members.

Another new challenge that arises from genomic research is that some risks may extend beyond individuals to an entire population. This can happen when DNA data sets are constructed around relatively homogenous populations to increase the chances of detecting genetic variation within the less than 0.1% deviation that exists between any two persons in the world. Any benefits population-based genomic research presents must be weighed against the possibility of stigmatization and discrimination.

These considerations make it necessary to examine whether current standards that govern research can minimize the risks inherent to genomic research and sufficiently protect individual subjects as well as populations adequately.

Uses of the Data

In addition to acknowledging concerns that arise from the nature of the information archived in genomic databases, it is necessary to address intended uses of DNA material. Participating individuals and groups may have reservations about their information being utilized for certain types of research projects. Therefore, it is important that subjects have the opportunity to be informed about, evaluate, and consent to the goals of the intended research.

THE STRUCTURE OF CONSENT

Population-based genomic research raises the question of whether consent need be obtained solely from individuals or whether review by the target population is needed as well. The concept of community review, also referred to as community consultation, may prove to be a successful method to minimize harm to certain groups and to help identify community support for population-based research endeavors. When a community is opposed to the research, the study should not be conducted. When a proposal is met with support from the community, it nevertheless remains important to obtain individual subjects' consent. Community consultation cannot be used as a substitute for informed consent. Instead, it should precede and complement the process, serving as an opportunity to begin educating members of the group from which research subjects will be drawn.

Informed Consent

Though an imperfect safeguard, self-determination through informed consent has been considered an important mechanism to protect subjects from abuses in research. When the process is carried out properly, it should prepare individuals to identify, understand, and consider the relevant risks and benefits that a research protocol presents. As a result of the new challenges that genomic research poses, additional safeguards may be necessary to address risks that arise from archived information and subsequent studies.

Consistent with the informed consent process in any type of human subjects research, subjects in genomic research should be informed of the: (1) purpose of the research; (2) overall risks and benefits associated with participation; (3) possible clinical findings that may result from the research and whether they will be disclosed to subjects; (4) possibility for commercial gain from the research endeavor (as addressed in Opinion 2.08 of the Council on Ethical and Judicial Affairs); (5) possible conflict of interests that investigators face (as discussed in Opinion 8.0315); and (6) right to withdraw from the research at any time.

In addition, disclosure should include information regarding: (1) measures to protect privacy; (2) the scope of any additional research foreseeable at the time the sample is collected; and (3) the time and manner in which archived information and samples will be discarded.

With regard to privacy, subjects should be told whether their materials will remain *identified* (i.e., will contain personally identifiable information such as their name or social security number). The confidentiality of their materials will be protected more completely, however, if data are stripped of all identifiers (i.e., *de-identified*). One shortcoming with this method is that completely de-identified information and samples lose some of their application. Instead, it is customary to code personal identifiers, such that only the investigator can trace material back to specific individuals (i.e., *coded* samples).

Coding may be useful if it is anticipated that subjects may wish to learn of relevant findings and, therefore, will need to be contacted. Use of coding also allows subjects to remain easily accessible to enroll in subsequent research. More importantly, it gives subjects the option to remove their information and samples from the database if they decide to withdraw from the investigation. De-identified samples, while they offer greater protection of confidentiality, do not have any such flexibility.

Discussing foreseeable future genomic research with potential subjects enables them to evaluate and decide whether participation in the overall investigation is consistent with their moral beliefs and personal preferences. It is paramount that subjects understand, from the disclosure process, the nature of the protocol in which they are enrolling, namely whether the material will remain personally identified, be coded, or be completely de-identified. In addition, if data are to remain identified or coded, subjects should be told whether they can expect to be contacted in the future to share in findings or to consider participating in additional research, which may relate to the current protocol or extend to other research purposes. Individuals should always be free to refuse the use of their biological materials in research, without penalty.

Waiver of Consent

According to the American Society of Human Genetics' (ASHG) official statement on informed consent for genetic research, it is inappropriate to obtain a subject's blanket consent for the use of their archived information and samples in subsequent research if these materials contain information that can identify the individual.

The National Bioethics Advisory Commission (NBAC) takes a different position. Assuming an analogy between the materials contained in DNA databanks and healthcare data recorded in medical records, its standards reflect federal regulations that allow research to proceed without the requirement of obtaining consent from subjects, where participation risks are no more than minimal. This position has drawn criticism from commentators who stress the unique nature of risks associated with genetic information. It is their belief that federal regulations, which were written mostly to anticipate physical risks, do not provide an adequate framework to protect subjects in genomic research.

Finally, the argument can be made that even de-identified materials--whether newly or previously collected--should not be used in ways to which subjects did not specifically consent. Based on the principle of respect for autonomy individuals can refuse to participate or to have their information used in research that is contrary to their values and preferences.

Presumed Consent

Under the presumed consent standard that Iceland has adopted, the willingness of an individual to participate in research is assumed unless the individual takes appropriate measures to formally opt out. However, this standard can only function as an effective safeguard if concerned individuals are informed of:

- the risks and benefits associated with the proposed research;
- the fact that participation is optional (i.e., individuals who choose not to participate will not be penalized for their decision);
- the appropriate steps to follow in order to opt out;
- their status as subjects unless they formally opt out; and
- the contact information for a person who can provide them with further clarification and answers to their questions.

This model of presumed consent for participation in research has never been proposed in the United States. However, it has been adopted in Iceland where it is the source of some controversy. A genetic company was granted a twelve year exclusive license by the Icelandic government to extract information from the Iceland Health Sector Database (HSD). A majority of Icelandic people voted in support of the creation of the database during a referendum, as a community consent process. As a result, competent Icelandic people are presumed willing to have information from their medical records entered into the database, unless they take necessary measures to opt out of the HSD.

None of the guidelines that govern the practice of research in the United States permit use of the standard of presumed consent as an alternative to informed consent. In fact, the general attitude towards presumed consent seems to be that it is inconsistent with the principle of autonomy, upon which ethical protections for research subjects are built. This sentiment may change if developments in genomic research suggest that highly important and unique opportunities to gain new knowledge are being missed. Pressure toward change may come from the biotechnology industry if it becomes too cumbersome to conduct research that fulfills the informed consent requirement.

CONCLUSION

The use of DNA databanks for genomic research raises new scientific possibilities as well as new challenges. Suggestions have been made to relax the standards that govern research, in an attempt to promote the acquisition of valuable information, although the need for strict interpretation of informed consent may be needed to protect subjects and the communities from which they are drawn from new forms of risks. Without proper education of potential subjects, genomic research may face severe setbacks. Therefore, it is imperative that physicians be prepared to discuss with their patients and/or potential subjects this new biomedical revolution.

RECOMMENDATIONS

The Council recommends that the following be adopted and the remainder of the report be filed:

The following safeguards should be applied to the use of databases for the purpose of population-based genomic research:

1. Physicians who participate as investigators in genomic research should have adequate training in genomic research and related ethical issues so as to be able to discuss these issues with patients and/or potential research subjects.

2. If research is to be conducted within a defined subset of the general population, that is, an identifiable community, then investigators should consult with the community to design a study that will minimize harm not only for individual subjects, but also for the community. When substantial opposition to the research is expressed within the community, investigators should not conduct the study. When the community supports a proposal, investigators nevertheless should obtain individual consent in the usual manner. The same procedure should be followed whether the investigators intend to collect new samples and data or whether they wish to use previously archived data sets.

3. When obtaining the informed consent of individuals to participate in genomic research, standard informed consent requirements apply (see Opinion 2.07). In addition:

   (a) Special emphasis should be placed on disclosing the specific standards of privacy contained in the study: whether the material will be coded (i.e., encrypted so that only the investigator can trace materials back to specific individuals) or be completely de-identified (i.e., stripped of identifiers).
   (b) If data are to be coded, subjects should be told whether they can expect to be contacted in the future to share in findings or to consider participating in additional research, which may relate to the current protocol or extend to other research purposes.
   (c) Individuals should always be free to refuse the use of their biological materials in research, without penalty.
   (d) Disclosure should include information about whether investigators or subjects stand to gain financially from research findings (see Opinion 2.08). Such disclosure should refer to the possible conflicts of interest of the investigators (see Opinion 8.0315).
   (e) Subjects should be informed of when, if ever, and how archived information and samples will be discarded.

4. To strengthen the protection of confidentiality, genomic research should not be conducted using information and samples that identify the individuals from whom they were obtained (i.e., by name or social security number). Furthermore, to protect subsets of the population from such harms as stigmatization and discrimination, demographic information not required for the study's purposes should be coded.

(References pertaining to Report 4 of the Council on Ethical and Judicial Affairs are available from the Division of Ethics Standards.)

5. A DECLARATION OF PROFESSIONAL RESPONSIBILITY

HOUSE ACTION: RECOMMENDATION ADOPTED AND REMAINDER OF REPORT FILED

MEDICINE'S RESPONSE TO THREATS TO HUMAN HEALTH

Bioterrorism, the AIDS pandemic, and the potential misuse of genetic science pose unprecedented threats to the health and well-being of humanity. While these threats are new, medicine's response to these challenges is guided by a centuries-old ethic of caring for the sick and the suffering.

In light of these new threats, the AMA is positioned to lead the world community of physicians in joining together across geographical and political divides in a public recommitment to medicine's guiding principles. The *Declaration of Professional Responsibility: Medicine's Social Contract with Humanity* (see Appendix) is an instrument for demonstrating that unity. The *Declaration* affirms (1) the ideals that, throughout history, have motivated individuals to enter the profession of medicine, and (2) the conduct that has given life to those ideals and earned society's trust in the healing profession.