69. Genetic research in large populations

Taken from a position paper published in 2003

The decision in the Israeli Medical Association to set up a committee to address the subject of genetic research followed a series of events related to genetic research in Israel, which raised fundamental questions regarding the conducting and management of genetic research, especially in designated large populations. These questions are new, and it was impossible to find existing answers in legislation or accepted ethical codes.
Recently, a commercial company began collecting blood samples on a large national scale in an attempt to map the genes of hereditary illnesses in members of a specific ethnic group. The subject aroused considerable public interest and led to a sharp debate on the sensitive issues surrounding the confidentiality of genetic information, the genetic marking of an ethnic group, commerce in genetic information, and the status of the physician vis-a-vis the commercial company conducting the research on the one hand and the individual patient on the other hand.
As a result, the Ethics Board of the Israeli Medical Association decided to set up a multi-disciplinary committee of specialists, to formulate recommendations regarding the conduct of genetic research on large populations and the treatment of the results obtained.
At the outset, the committee wishes to emphasize that the discussions held and the summary presented in the report do not refer to the activities of any specific company or researchers. The entire report should be read as containing recommendations and directions both for the entities that engage in genetic research, with emphasis on physicians, and for the entities who determine policy, with the aim of formulating rules with a binding normative weight.
Thanks are due to the members of the committee for the considerable time that they devoted to the discussions, for their sensible advice, and for their contribution to clarification of the complex subjects on which this document is based. Special thanks are due to Advocate Assaf Toib, the legal advisor of the Ethics Board, for his faithful help in drafting the first version, and to members of the legal department who helped him, to Prof Zvi Borochovitz and to Dr Carmel Shalev for their sharp input into the final wording of this document.

Definition of the major terms in the report

The following are definitions of major terms used in writing the report:

- Population – All individuals associated with a group of persons having a common denominator.
- Large populations – Persons associated with a population group that contains a large number of individuals having a common denominator (ethical, medical, or other).

- Genetic test – A test of DNA or its products of a person, for the characterization and comparison of DNA sequences or research on the genetic material of the person, in order to locate tendencies to a specific illness or for confirmation of a diagnosis of a genetic illness.
- Population genetics – Research on the degree of variation in a group of individuals.
- Genetic material – A gene, genetic products or functioning, or analysis of DNA or chromosomes.
- Genetic research – Research in which tests are made of a gene, genetic products or functioning, or analysis of DNA or of chromosomes, for the purpose of location or negation of a mutation connected to a genetic illness.
- Genetic information – Information obtained as a result of genetic research.
- Ethnic group – A group of persons recognized as such on the basis of unique characteristics, such as blood, genealogy, language, culture, or nationality.

The aim of the report

The document is primarily intended to formulate rules of ethical conduct for physicians who participate in genetic research. The report also contains recommendations related to research physicians conducting the research, on one hand, and commercial companies that engage in genetic research on large populations, on the other hand. We are aware that these can only serve as recommendations for the commercial companies, but their acceptance will considerably facilitate cooperation with the medical community and, in the final analysis, will advance genetic research.
The report was written before legal tools for regulation of genetic research on large populations were formulated. We hope that this report will advance the process of formulating normative rules for what is "permitted" and "forbidden" in genetic research and will form a basis for legislation that will lead to regulation of this subject.

The starting points for the recommendations of the committee

The recommendations of the committee are based on the following starting points:

a) The committee recognizes the importance of genetic research and calls on all entities to take steps to advance it.
b) Genetic research in large, specified populations, in contrast to research on individuals, creates a new set of ethical, moral, and legal issues that did not exist until now.
c) Therefore, concomitant with the rapid development of genetic research, we must prepare the ethical and legal tools required for supervision of this research.
d) The committee recognizes the aspiration of commercial companies engaging in research of this kind to enjoy an economic profit, provided that the good of the public is also maintained, including improvement of medicine and medical research.

e) In genetic research conducted on large populations, care must be taken to respect the rights and privacy of the patient or individual being researched, and to avoid the creation of a negative characteristic (stigma) regarding the entire population researched.

f) It is best to conduct genetic research in large populations in cooperation with the medical community and to regard physicians as partners to the research, and not merely the suppliers of samples.

g) The advancement of bio-medical research obligates global cooperation including the transfer of information and samples between various countries. Limitations should be set for the transfer of such information when dealing with information regarding large populations of residents.

General principles

1. Genetic research on humans, like any other research, shall be subject to both the law and the ethical code and shall obligate the receipt of all the obligatory approvals, including approval by the supreme Helsinki committee for genetic trials on humans.
2. The public should be informed about genetic research being conducted on large populations. Such publication will ensure transparency, supervision, and public discussion of the research. Exceptions are those cases in which the very act of publication may harm the entity conducting the research or the population being researched.
3. Residents of the State are not a "national resource" or the "property" of the State, and neither is their blood and the genetic material derived from it. However, the State is a "stakeholder" in genetic information related to its population. This leads to the right of the State to formulate rules for the management of the research and the use made of the genetic information collected.
4. Every publication of the results of genetic research conducted on large populations shall be done with maximum sensitivity in order to prevent negative characterization or stigmatization of the population being researched.
5. For the benefit of overall human knowledge, the publication of the results of the genetic research should be encouraged even if they do not meet the expectations of the researchers or the commercial company conducting the research.

Setting up a statutory entity for genetic research

The committee calls on the State to set up a statutory entity for genetic research whose functions shall be:

1. To approve the execution of genetic research in general and on large populations in particular.

2. To supervise execution of genetic research, including scientific supervision and confidentiality of the accumulated information.
3. To formulate the rules for transfer of the overall genetic information and its secondary uses, as a scientific or economic asset, to a third party, including multi-national pharmaceutical companies.
4. To formulate rules for approval of the purchase or merger of a commercial company conducting research with other companies and entities in cases in which there is concern that the genetic information collected will be misused.
5. To specify a period of time for execution of the research, at the end of which the information shall enter the public domain.
6. To formulate rules for saving genetic information and blood samples in the event the activities of the researchers or of the commercial company conducting the research 7. To take steps to set up a national DNA bank that will be available to the medical and scientific community in Israel.
8. To verify that blood samples and genetic information will not be destroyed at the end of the research or on dissolution of the company, and that they will be transferred to the national DNA bank in accordance with the rules to be formulated.
9. To verify that if the company conducting the research is purchased during or after the trial by another company, the purchasing company shall assume all the commitments assumed by the first company regarding management of the research and the genetic bank held by it.

Informed consent for medical trials and genetic research

The obligation to receive informed consent for any action connected to or affecting one's body, or for use to be made of parts of one's body, including organs, tissues, and blood, is derived from a person's rights over his body.
This obligation applies even more stringently in connection with medical trials and genetic research. Genetic research has broad potential to expose private information about a participant in a trial, his family, offspring, and ethnic group, and even about large populations about which, until now, it was impossible to collect genetic information.

1. As part of the process of obtaining a patient's informed consent for execution of genetic research, the patient shall be permitted to choose one of two options:

   a) The granting of "general consent" – Sweeping consent given for every future research use of a sample taken from the research subject, without the need to return to him to receive repeated consent, provided that every research conducted based on the material collected aims to advance science and medicine. This general consent shall not be given by minors and/or legally incompetent persons and/or their guardians.

b) The granting of "individual consent" – Consent by the person researched for execution of a specific research or trial or in a specified field, so that in the event of expansion of the research or the execution of new research, application must be made again to the person researched in order to obtain his consent for the new research. Without such renewed consent, no use may be made of the information received and/or of the samples.

2. Clinical trials involving persons lacking legal competence to give informed consent shall be performed only in the absence of alternative research groups. Such a case requires the informed consent of the guardian responsible for the legally incompetent subject. An additional condition for research on legally incompetent groups of people is that the research seeks to advance the health of the "population represented" by such people.

3. Research in large, specified, population groups obligates the entity conducting the research to obtain, in addition to individual consent, also "collective informed consent". This consent may be given by the "natural" leaders of the said group.

4. Informed consent shall also be given for the manner in which the information is stored: as unidentified information or as coded information that may be identified.

The obligation of disclosure by a physician taking part in the trial

1. As part of the process of obtaining informed consent, a physician involved in a clinical trial shall inform the research subject of his degree of involvement in the proposed research. The physician may be involved in the research as follows:

- Research physician – A physician who actively participates in the execution of the research over its entire length.
- A physician who participates in the research – A physician who makes an intellectual contribution to the planning of the trial, its execution, and the analysis of its results, but does not accompany the research during all its stages.
- A physician who is a research agent – A physician who constitutes an "agent", who transfers the genetic sample to a commercial company for the purpose of the research.

2. The research subject shall be informed, in language comprehensible to him, that the research in which a commercial company is involved contains a chance for financial profit by the company.
3. The research subject shall be informed that a research agent receives financial remuneration for his services from the commercial company conducting the research.
4. The research subject shall be informed of the precise aims of the research and its ramifications, if any, on the research subject, his family, offspring, and the population

group to which he belongs.

5. The research subject shall be informed if there is intent to transfer the information or samples collected to any third party whatsoever, during or after the trial.
6. The research subject shall be informed of the personal benefit to him and to his family, if any, which will emerge from his participation in the research.
7. The research subject shall be informed at the end of the trial of the results, including drugs or medical technologies developed during the trial. In the case of an unidentified examinee, this shall be done by publication in a daily newspaper.

Medical confidentiality

1. Information regarding a person who participates in a trial may not be furnished to anyone else, including members of his family, unless his express consent has been received:
   - To reveal the very fact of his participation in the research.
   - To reveal the personal results received from the research.
2. A person who participates in a trial shall be informed confidentially by his physician of the results of the research affecting him personally, if this research was done using identified DNA.
3. Both the research subject and members of his family reserve the right not to know the results of the trial and its ramifications on him and on his family.

Expansion of the genetic research

Sometimes the need arises to expand medical research by adding additional relatives, expanding the use of a sample beyond that agreed in advance, or including an additional research entity in the examination of an existing sample. In such cases, the following actions shall be taken:

1. Any change to the scale or aims of the trial obligates advance approval from the Helsinki committee that approved the original trial.
2. The research subject himself shall appeal to additional relatives where relevant. With the subject's consent, his physician may do so instead.
3. Expansion of the use of a sample beyond that agreed in advance obligates the receipt of renewed informed consent in those cases in which only "individual", rather than "general" consent was given.
4. The transfer of information and samples between academic-public research entities is permitted without limitation as long as the information is transferred for the advancement of science only and subject to the consent of the research subject.
5. The transfer of information between commercial entities obligates approval by

the Supreme Helsinki Committee for genetic trials on humans, and, in the future, approval by the statutory authority to be set up for this purpose.

6. The removal from Israel of genetic information that originates in large populations shall be permitted only after receipt of approval from the Supreme Helsinki Committee for genetic trials on humans, and in the future, approval by the statutory authority.

Participation of physicians in the research

1. Physicians who participate in the conducting of the research shall be entitled to access to the information collected in the research.
2. Every physician who participates in the research shall be entitled to conduct a dialog with his colleagues to the research or with the commercial company conducting the research, in which he may put forward proposals and ideas of his own regarding the research.
3. In general, a connection with a physician who is a "physician participating in the research" is preferable to a physician who is a "physician agent".
4. Remuneration for a physician employed in an academic or public institution who participates in the conducting of genetic research shall be given solely by means of the institution employing him. A physician who works privately shall be entitled to receive remuneration for his contribution to the research.

Rights to the genetic information

An increasing part of genetic research focuses on epidemiological genetic research on large populations. This fact has broad significance that goes beyond the level of the individual and may influence a large number of populations up to the level of the State itself. Naturally, research of such magnitude obligates different treatment from that which was customary until now. Consequently:

1. The State is forbidden to trade in genetic samples or genetic information, similar to the prohibition to trade in organs for transplanting.
2. The collection of genetic information and samples within the State is possible thanks to the cooperation of citizens of the State. Although this contribution does not give title to the State, it creates a link to the information.
3. The State has the right to prohibit use of genetic information and to set limits for its use, including the formulation of rules aimed at protection of populations and groups of individuals.

The fruits of the genetic research

The balance required between the economic interest of the commercial company conducting the research and the welfare of the community obligates the formulation of

new rules that will secure both parties.

1. It is proper that the community cooperate with the commercial company conducting the research for advancement of medical research and medicine.
2. The community that contributes the human resources constituting the basis for the genetic information shall be entitled to demand remuneration from the fruits of the research.
3. The remuneration for patients who participated in the trial, except in the case of research in unidentified DNA, shall be as far as possible the supply of free drugs or medical technologies, the products of the research.
4. The remuneration for the general community shall be a financial one, as an agreed proportion of the research budget or its income.
5. Financial remuneration shall be given for advancement of medical research of those medical or research institutions that participated in the trial or for advancement of public health.
6. The economic remuneration for the State shall be stipulated in advance and shall not be on a voluntary basis.