Conclusion

This document is intended to provide guidance to investigators and IRBs who are involved in large-scale sequencing efforts. It is designed to alert them to special ethical concerns that may arise in such projects. In particular, it provides guidance for the use of existing and the construction of new DNA libraries. Adhering to this guidance will ensure that the initial version of the complete human sequence is derived from multiple, diverse donors; that donors will have the opportunity to make an informed decision about whether to contribute their DNA to this project; and that effective steps will be taken by investigators to ensure the privacy and confidentiality of donors.

Investigators funded by NCHGR and DOE to develop new libraries for large-scale human DNA sequencing will be required to have their plans for the recruitment of DNA donors, including the informed consent documents, reviewed and approved by the funding agency before donors are recruited. Investigators involved in large-scale human sequencing will also be asked to observe those aspects of this guidance that pertain to them.

Approved August 17, 1996, by:

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Footnotes

1. Office of Protection from Research Risks, Protecting Human Research Subjects: Institutional Review Board Guidebook (OPRR: U.S. Government Printing Office, 1993).

2. It is recognized that it will be trivially easy to determine the sex of the donor of the library, by assaying for the presence or absence of Y chromosome in the library.

3. There are a number of approaches to preventing a DNA donor from knowing that his/her DNA was actually sequenced as part of the HGP. For example, each time a clone library is to be made, an appropriately diverse pool of between five and ten volunteers can be chosen in such a way that none of them knows the identity of anyone else in the pool. Samples for DNA preparation and for preparation of a cell line can be collected from all of the volunteers (who have been told that their specimen may or may not eventually be used for DNA sequencing) and one of those samples is randomly and blindly selected as the source actually used for library construction. In this way, not only will the identity of the individual whose DNA is chosen not be known to the investigators, but that individual will also not be sure that s/he is the actual source.

4. Although recontacting donors should not be possible, investigators will potentially want to be able to resample a donor's genome. Thus, at the time the initial specimen is obtained, in addition to making a clone library representing the donor's genome, it should also be used to prepare an additional aliquot of high molecular weight DNA for storage and a permanent cell line. Either resource could then be used as a source of the donor's genome in case additional DNA were needed or comparison with the results of the analysis of the cloned DNA were desired.

5. There has been discussion in the scientific community about the sex of DNA donors. A library prepared from a female donor will contain DNA from the X chromosome in an amount equivalent to the autosomes, but will completely lack Y chromosomal DNA. Conversely, a library prepared from a male donor will contain Y DNA, but both X and Y DNA will only be present at half the frequency of the DNA from the other chromosomes. Scientifically, then, there are both advantages and disadvantages inherent in the use of either a male or a female donor. The question of the sex of the donor also involves the question of the use of somatic or germ line DNA to make libraries. For making libraries, useful amounts of germ line DNA can only be obtained from a male source (i.e., from sperm); it is not possible to obtain enough ova from a female donor to isolate germ line DNA for this purpose. Opinion is divided in the scientific community about whether germ line or somatic DNA should be used for large-scale sequencing. Somatic DNA is known to be rearranged, relative to germ line DNA, in certain regions (e.g., the immunoglobulin genes) and the possibility has been raised that other developmentally based rearrangements may occur, although no example of the latter has been offered. While some believe that the sequence product should not contain any rearrangements of this sort, others consider this potential advantage of germ line DNA to be relatively minor in comparison to the need to have the X chromosome fully represented in sequencing efforts and prefer the use of somatic DNA.

6. Individuals whose DNA was used for library construction (with the exception of those created from deceased or anonymous individuals) should be fully informed about the risks and benefits described above, should freely choose whether they would like their DNA to continue to be used for this purpose, and their decision should be documented.