# REPORT
# OF THE

# SPECIAL EMPHASIS PANEL
# ON

# OPPORTUNITIES AND OBSTACLES TO GENETIC RESEARCH in NHLBI CLINICAL STUDIES

# CONTENTS

# FOREWORD

NHLBI-supported population-based studies, clinical trials, and other clinical investigations, both investigator- and Institute-initiated, offer special opportunities for genetic research. The availability of stored genetic material collected from individuals who are rigorously phenotyped according to standardized protocols provides an unprecedented resource to examine putative genetic factors in relationship to clinical or subclinical disease and its risk factors. The ability to link the wealth of phenotypic information collected in these studies with genotypic information measured at some later point presents an extremely cost-effective approach for discovering new genetic factors, for confirming initial reports of candidate genes, and for correlating interventional outcome with genetic architecture. The comprehensive, standardized, and rigorous nature of their phenotypic information makes them outstanding resources in which to explore the genetic and environmental bases of heart, lung, and blood diseases and to observe relationships between clinical outcome and genotypic composition.

A recent inventory of NHLBI blood samples indicates a large potential. For example, in the Division of Epidemiology and Clinical Applications alone, NHLBI-initiated studies (both observational studies and clinical trials) have collected or will collect genetic material from more than 50,000 subjects of diverse ethnic and racial backgrounds. Tens of thousands of other subjects will soon be added in upcoming interventional studies, some or all of whom may be appropriate for genetic investigations. Of immeasurable value and critical for successful genetic analysis of complex diseases, these studies use rigorously standardized methods to extensively characterize risk factors and other phenotypic characteristics. Certain studies also have the additional advantage of long-term follow-up.

In order for NHLBI-supported studies to respond effectively, quickly, and in a coordinated fashion to opportunities for genetic research, a significant number of serious potential impediments and issues must be addressed, ranging from informed consent to prioritizing and expediting requests for access to stored samples. As a consequence, the NHLBI convened a Special Emphasis Panel (SEP) on the Opportunities and Obstacles to Genetic Research in NHLBI Clinical Studies to chart a course for future research efforts. The SEP was charged to:

- Address the critical issues, barriers, and needs to permit optimal use of collected clinical samples.

- Address issues relating to collecting and sharing samples in future NHLBI studies.

- Recommend a comprehensive master plan of activities to facilitate genetic studies in NHLBI clinical research.

This document is intended to serve many purposes. One is to guide the decision-making process of the National Heart, Lung, and Blood Advisory Council.

Another purpose is to inform the Nation's scientific investigators of possible areas of opportunity. The plan will also inform members of Congress of research progress and future research directions within the purview of the NHLBI. In addition, the document will assist the Institute in its day-to-day operations by providing clarity and direction to the growth of NHLBI-supported research efforts in genetics.

We are extremely pleased to have this SEP report to foster and facilitate the evolution of the molecular genetics of heart, lung, and blood diseases, and we are grateful to the SEP members for this most valuable contribution.

CLAUDE LENFANT, M.D.
Director

# OVERVIEW

Biomedical science is poised to uncover, early in the 21st century, many of the genetic factors that modulate the risk of heart, lung, and blood diseases. Such insight will surely point to important biochemical mechanisms, and will also facilitate the study of the role of environmental risk factors.

The scientific foundations for such studies flow from breakthroughs in molecular genetics, including the Human Genome Project and technologies for DNA analysis. However, such laboratory tools constitute only half the battle. Successful genetic investigation of human disease also requires the availability of first-rate clinical epidemiological collections, consisting of carefully phenotyped patients and family members.

Over the past decade, NHLBI has invested, and continues to invest, in a broad array of clinical data collection projects—both investigator-initiated and Institute-initiated. Recognizing the great importance of such resources, NHLBI convened this Special Emphasis Panel (SEP) to study whether the appropriate steps were being taken to ensure maximal benefit from these resources. The Panel's membership drew from the community of experts in heart, lung, and blood diseases, as well as experts in genetics, epidemiology, clinical investigation, and ethics.

The key issue was: How could NHLBI's valuable data and sample collections be made available to the broadest community of scientific investigators while maintaining the privacy and trust of the study participants? What barriers (of funding, of sample limitation, of control) existed and how could they be overcome?

The SEP identified four key areas in which action was needed:

1. *Disseminating information about genetic studies.* At present there is no systematic way for scientists to easily get information about the large number of different studies and stored samples or to discover if the appropriate resource exists to test important new hypotheses. Maximizing the impact of these resources requires minimizing the barriers to information.

2. *Ensuring adequate DNA resources.* Many studies have only a limited quantity of DNA available, necessitating rationing. This limitation could be removed by the preparation of immortalized cell lines, if such capability could be provided to the projects.

3. *Facilitating collaboration.* Maximizing utility of collections requires maximizing collaboration and access. Realistically, this requires setting in place the appropriate incentives and mechanisms for investigators to work together.

4. *Protecting human subjects.* In addition to all other aspects of protecting human subjects, there needs to be adequate informed consent from participants. It is important to develop and use informed consent documents that maximize

both personal protection and broad scientific research.

The SEP performed much of its work through four subcommittees focused on these four topics. The SEP and its subcommittees performed their tasks by numerous conference calls. The SEP members met in Washington, DC, on February 5, 1997. The SEP also sought input from investigators involved in population studies, especially those that work with minority or underrepresented populations, by circulating a prepublication draft of this report. Comments were used to guide the preparation of the final report. Specific comments and ideas were incorporated wherever it was feasible.

The SEP's report is organized around the four key topics noted above. Each section makes specific, implementable recommendations to NHLBI. Among its principal recommendations, the report calls for NHLBI to

- Create and curate a Web site providing easy access to layered information about the major study collections.
- Support a centralized service to create, store, and distribute immortalized cell lines.
- Appoint a standing Specimen Resource Advisory Board to assist NHLBI in management of the above activities.
- Provide necessary funding to facilitate collaborations between new investigators and existing large collections.
- Facilitate the use of appropriate informed consent procedures.

We emphasize that these recommendations are meant to facilitate, not force, sharing of resources and collaboration among investigators. We recognize that some of these recommendations may require substantial funding. We also recognize the many demands on the NHLBI budget, but we believe that such spending is well-justified. We have not, however, proposed specific amounts to be spent. The appropriate funding will need to be determined by the NHLBI leadership, in consultation with the Specimen Resource Advisory Board.

As co-chairmen, we want to express our deepest thanks to the members of the SEP for their considerable work over the course of the past year. We also are deeply grateful for the tremendous effort of NHLBI staff, particularly Drs. Susan Old and Stephen Mockrin. Finally, we thank the NHLBI itself for its foresight in supporting genetic collections in the past and in trying to maximize their utility in the future. The current efforts are laying the foundation for the next century of research and medical advances.

Eric Lander, Ph.D.
Roger R. Williams, M.D.
*Cochairs*
Special Emphasis Panel on Opportunities and Obstacles to Genetic Research in NHLBI Clinical Studies

# DISSEMINATING INFORMATION ABOUT GENETIC STUDIES

## INTRODUCTION

The NHLBI has supported and continues to support a large number of clinical investigations, both Institute-initiated and investigator-initiated. Many of these studies include a wealth of phenotypic information that may provide the basis for genetic investigations. Indeed, a partial inventory of Institute-supported studies reveals over 100 different studies with potential for genetic investigations. The availability of stored specimens from these population-based studies, clinical trials, and other clinical investigations offer unique opportunities for genetic research. Capitalizing on this opportunity requires maximizing knowledge about and access to these unique resources.

## ISSUES

Ideally, an investigator interested in a collaboration involving NHLBI specimens should be able to quickly access the relevant study information, identify appropriate phenotypes, genotypes, and genetic material, and rapidly move to develop a collaboration based on the appropriate contact persons for a specific study. Presently, the NHLBI has no centralized database that captures this information and disseminates it to interested investigators. Under the best of circumstances, the information would be current and the access would be universal. In practice, however, the challenge facing an investigator who wishes to identify and access appropriate studies and samples to address a genetic question is currently a daunting one.

## SOLUTIONS

The most cost-effective way to disseminate information about potential resources for genetic studies is to provide investigators with immediate access to this information through a World Wide Web site as part of the NHLBI home page. The purpose of the Web site would be to inform the scientific community of possible scientific collaborations, not to store or release scientific data. This Web site would provide a layered approach to information about phenotypes and stored samples in a comprehensive and easy-to-use manner that would lead the investigator ever more deeply into the methodology for phenotyping and specimen availability. After reviewing several levels of Web page information, appropriate articles, and protocol information, a researcher could decide whether to go forward with contacting the study investigators with regard to a potential collaboration. The Web site should identify a responsible contact person. For NHLBI contracts and cooperative agreements the contact person should be the NHLBI project scientist, and for investigator-initiated grants the contact person should be the Principal Investigator for the parent study.

A multilevel approach to information on the study and its samples is suggested. The top layer would consist of general information about the study, including: title of the study, NIH grant number, types of participants (e.g., families, sib-pairs, randoms, ethnic group, special population information), types of samples (e.g.,

frozen DNA, plasma, whole blood, tissues), number of samples of each type of participant (e.g., 1,000 individuals or 500 sib-pairs), phenotypes collected (e.g., clinic measures, lab measures, environmental measures), genetic nature of the study (e.g., is any genetic analysis planned or been performed on these specimens?), individuals to contact (e.g., the Principal Investigator of the parent study and the NHLBI program official), informed consent (e.g., is there consent to do genetics, to share the samples, to recontact subjects?). The second layer of information may contain some additional details of the study, such as the grant application abstract, study design information (e.g., portions of the Manual of Procedures, references to manuscripts), the complete informed consent form(s), and links to an institution Web page. A panel of experts should be convened by the NHLBI to give advice and guidance in compiling this information.

**RECOMMENDATIONS**

1.1 NHLBI should establish a Specimen Resource Advisory Board to provide oversight and advice to the NHLBI. A subcommittee of this Advisory Board should provide guidance on information dissemination and Web page management. Additional subcommittees of this Board should be established as recommended later in this document (Recommendations 2.2, 2.3, and 4.3). This Advisory Board should include individuals well-acquainted with informed consent issues, genetics, genomics, population-based studies, and heart, lung, and blood diseases.

1.2 The NHLBI, with the above Advisory Board, should identify studies to be included in a stored sample research data base on a Web page. These studies should be prioritized for inclusion on the Web page by the quality and quantity of their phenotypes and genetic material. Although this identification process should be as broad as possible, priority should be given to studies with high-quality data and potential for genetic investigations. Eventually, all NHLBI-funded studies of greater than approximately 150 people could be listed. The Web page should be developed over a 12-18 month period. The Web page should be updated on a yearly basis and the progress report mechanism should be used to provide updated information.

1.3 To gather the data to be included on the Web page, the NHLBI should require investigators to prepare an electronic data sheet for their entire study, including, but not limited to, information on study title and NIH number, mechanism of support, study design, number of samples, type of samples, DNA quality, clinical phenotypes, brief research protocol, informed consent, published manuscripts, Web links, and telephone, fax, and e-mail contact numbers. The precise content should be specified by NHLBI in consultation with the Specimen Resource Advisory Board. This data sheet could be updated on an annual basis, or as needed.

# ENSURING ADEQUATE DNA RESOURCES

## INTRODUCTION

A number of the large NHLBI-sponsored studies have established data bases combining extensive phenotypic characterization of subjects and longitudinal follow-up of clinical outcome. These populations and data sets provide unique resources for molecular genetic studies of inherited susceptibility to specific cardiovascular, pulmonary, and hematologic diseases. These patient resources may hold the key to unraveling the pathogenesis of many of the common causes of morbidity and mortality in our society. Unfortunately, the amount of DNA available for use from past and ongoing studies is very limited, hindering advances in this area. NHLBI can facilitate and accelerate progress toward identification of disease susceptibility loci by prudent investment in renewable DNA resources at this critical time.

## ISSUES

There are four major issues bearing on the efficient and timely use of DNA resources. With existing technology, these issues can be overcome with an investment that constitutes a very small fraction of the cost that has gone into establishing these resources. This investment will be of major importance for determining the genetic contributors to common human diseases. The key issues are:

1. Very limited amounts of genomic DNA (e.g., 100-200 micrograms) are available from many study participants. Since typical experiments to test the impact of a molecular variant on a trait of interest require use of 100 nanograms to 1 microgram of DNA, these available DNA samples have been appropriately regarded as precious, finite resources. As a consequence, there has commonly been reluctance to expend an irreplaceable resource to test even compelling hypotheses in a timely fashion. It is anticipated that the number of variants that will warrant serious examination will expand enormously over the next several years, potentially exhausting these resources in a short period of time. The lack of availability of appropriate samples for testing hypotheses constitutes a major impediment to progress in this area.

2. Even when cell and DNA samples are available, funds are still needed to store, aliquot, and ship samples.

3. Appropriate incentives are needed for investigators in long-term studies to collaborate with outside investigators who have generated testable hypotheses.

4. Mechanisms must be established by which requests for samples from outside investigators can be evaluated and acted on in a timely fashion. It is recognized that use of these samples must acknowledge and respect the effort that has gone into data collection and maintenance.

Moreover, it must be recognized that specific areas of inquiry may be primary objectives of study investigators, and that outside requests that overlap with these interests must respect the interests of study investigators.

**SOLUTIONS**

The best approach is to establish a renewable source of DNA (that is, immortalized cell lines) from a large number of subjects from selected studies, and then to permit liberal access to these samples together with phenotype data, permitting investigators to test the impact of specific inherited variants on traits of interest. Moreover, the best way to accomplish the functions of receiving blood samples, preparing genomic DNA, establishing and growing immortalized cell lines, and storing and shipping of samples is in a dedicated centralized facility; this approach should be most economic and should maintain the highest quality.

A working model of such a resource is the set of 60, three-generation reference kindreds maintained by the Centre d'Etudes de Polymorphism Humain (CEPH). These family collections were established by an international consortium. Renewable sources of DNA from each family member were established and have been made generally available to the genetics research community. As a result, beginning in the 1980s, virtually all investigators wanting to localize new genes or genetic markers on the human genetic map used the identical resource, permitting accumulation of data across studies and, more importantly, putting a key resource in the hands of many investigators. This resource proved extraordinarily valuable, and catalyzed the development of genetic maps of the human genome. These genetic maps provided the cornerstone for initiation of the human genome project and provides a concrete example of the value of making such resources generally available.

The NHLBI can play a similar role in catalyzing identification of common human disease genes by providing a means for access to sample and data sets from large population-based and cohort studies. NHLBI will need to carefully consider which studies and samples are most critical to preserve for future investigations. Considerations include issues such as (1) the scope and quality of the phenotypic data collected; (2) the ethnic and gender composition of the study participants; (3) whether families have been studied; (4) the availability of subjects for resampling; and (5) the number of samples needed to provide adequate power for studies that may be contemplated in the near and long term.

In addition, a panel of experts will need to be convened by the NHLBI to identify specific sets of patient samples for immortalization in order of priority. Depending on the budget available for this effort, NHLBI can then identify the studies to be included.

Providing access to these DNA resources is a critical issue. It is important that these DNA resources and accompanying phenotypic data be made available to the broader scientific community to maximize

their impact. At the same time it is also important to recognize the scientific interests of investigators who have devoted careers to establishing and maintaining these resources. Hence, the NHLBI should establish a committee of experts to evaluate requests for access. The resources will have the greatest utility to the extent that barriers to access are minimized. To this end, NHLBI should strive to ensure rapid evaluation of requests with a minimum amount of paperwork.

Technical and cost issues involved in the establishment of immortalized cell lines are discussed in the Appendix at the end of this chapter.

**RECOMMENDATIONS**

2.1 NHLBI should establish renewable DNA resources by providing a centralized Immortalization and Repository Service for handling all aspects of the process, including DNA preparation, establishment of immortalized cell lines, aliquoting of samples, storage of DNA samples and cell lines, and shipping of samples to users. This facility should also organize and prepare data that will be disseminated with the samples.

2.2 As noted in Recommendation 1.1, the NHLBI should convene a subcommittee of the Specimen Resource Advisory Board to recommend to NHLBI which studies and associated data sets, and which samples from these studies are most suitable for this central immortalization repository. This subcommittee should include representatives with expertise in epidemiology, genetics, and heart, lung, and blood diseases. Immortalization of samples from past studies would typically require recontacting and redrawing of blood samples; this may be impractical or impossible for many studies, for reasons of both logistics and informed consent. Immortalization of samples from ongoing studies will pose many similar challenges. Ideally, immortalization should be prospectively included as a component of a study at its initiation.

2.3 NHLBI should convene an additional subcommittee of the Specimen Resource Advisory Board that will evaluate requests for access to DNA resources. This subcommittee should establish specific criteria for evaluation of requests, which are expected to include issues such as scientific merit, impact on available resources, and potential conflict with scientific goals of the parent studies from which samples will be drawn. Members of this subcommittee would include geneticists, representatives of the studies from which samples are collected, and NHLBI staff.

# APPENDIX:
# MECHANICS OF A RENEWABLE DNA RESOURCE

## 1. Preparation of Genomic DNA From Whole Blood

DNA preparation from venous blood provides an excellent yield of high-quality DNA that can be stored indefinitely. Starting with 20 milliliters of blood, the average yield is approximately 1 milligram of DNA. Cost of preparation and storage of samples is approximately $25 per sample. This represents the least expensive and quickest route to preparation of DNA. Some studies have used smaller amounts of blood or stored buffy coat samples, and have consequently obtained much smaller yields. Future studies should obtain larger amounts of DNA by emphasizing preparation of DNA from adequate samples of fresh blood; such preparation should be routinely included in the budgets of epidemiologic studies. This amount of DNA will meet many needs of the biomedical community and, in itself, would constitute a valuable resource.

## 2. Establishment of Lymphoblastoid Cell Lines—A Renewable Source of DNA

Beta lymphocytes are present in reasonably high concentration in venous blood. These lymphocytes can be immortalized by transformation with Epstein-Barr virus, providing immortalized cell lines that can be expanded at will to provide a renewable source of genomic DNA from study participants. Starting material for transformation is 10 milliliters of venous blood. Success with transformation averages 95% - 98% in experienced laboratories.

The cost of establishing an immortalized cell line and freezing-down the resulting samples for indefinite storage has been estimated, by laboratories that have established hundreds of cell lines, to be less than $90 per sample. These costs do not include expenses for shipping samples. If necessary, single samples can be shipped by overnight courier to the immortalizing laboratory at an average cost of $15; costs can be reduced by shipping many samples together or by locating immortalization cores on site, thereby eliminating shipping expenses.

In order to prepare DNA from a frozen cell line, the cell line is expanded in cell culture and DNA is extracted. Yield from a 200-milliliter culture is typically 1.5 - 3 milligrams of genomic DNA. Total cost for cell culture and DNA preparation is estimated at $75 per sample.

## 3. Shipping Samples to Investigators

Efficient use of DNA resources requires a reliable mechanism for shipping of aliquoted samples to study

investigators. Shipping of samples requires ability to aliquot and store samples in quantities sufficient to meet requirements. It is anticipated that most needs can be met by shipment of 1 microgram of genomic DNA, but that occasional uses may require larger samples. Samples can be aliquoted in many replicate sets at a single time and stored indefinitely prior to shipping. Once DNA samples are prepared, the cost of aliquoting and shipping a large set of samples is estimated to be $200 (for example, 10,000 samples of 1 microgram each in a microtiter plate format).

**4. Estimated Cost**

Cost estimates are based on the assumption that at follow-up visits for selected studies, 30 milliliters of venous blood would be drawn in acid citrate dextrose tubes; 20 milliliters would be used to prepare genomic DNA, with anticipated yield of 1 milligram, and 10 milliliters would be used to establish a lymphoblastoid cell line. At a future date, as needed, cell lines can be expanded and additional DNA prepared.

The total direct cost of preparing approximately 3 milligrams of genomic DNA from 10,000 subjects (1 milligram from whole blood, and 2 milligrams later from cell culture) plus the cost of shipping 1 microgram of each sample to 3,000 different investigators is estimated to be $2,600,000. These costs would scale linearly to increase or decrease the number of subjects included ($260 to provide 3,000 aliquots of each sample). Subsequent batches of 2,000 replicate sets could be prepared and shipped from frozen cell lines for approximately $1,150,000.

It is apparent that a substantial fraction of the expense incurred could be paid for by users of these resources. For example, receipt of a fee of $1,000 for each set of 10,000 samples would ultimately meet the direct cost of establishing and shipping the resource. This fee would not provide a financial hardship for most laboratories wanting to evaluate samples and would reduce the new NIH allocations required to support this endeavor. Special consideration could be given to highly meritorious requests for which this fee proved onerous.

# FACILITATING COLLABORATION

## INTRODUCTION

The NHLBI has supported major epidemiologic investigations of cardiovascular, pulmonary, and hematologic diseases that have generated large numbers of DNA samples and associated clinical data sets. Our growing knowledge of the human genome has created exciting new opportunities for determining the genetic basis of multifactorial human diseases. These opportunities have produced a dramatically increased demand for DNA samples and access to data sets from completed and ongoing epidemiologic investigations from new researchers who want to test hypotheses significantly different from those envisioned in the original study design.

## ISSUES

Completed epidemiologic investigations that no longer receive NIH funds frequently possess DNA samples with associated clinical data sets. Unfortunately, it can be difficult for new research to employ these valuable resources for new purposes that differ from the original study design, owing to the costs of sample maintenance and preliminary research studies, as well as the challenges of structuring collaborations among the original and new investigators. Ongoing epidemiologic investigations often experience similar problems in distributing samples and information to new collaborators examining hypothesis not included in the original study design. Three major issues must be addressed in order to facilitate collaboration and effective use of these stored samples:

1. Completed epidemiologic investigations usually do not possess funds to store DNA samples, ship samples to new investigators, or maintain associated data sets in easily retrievable form. In a similar fashion, ongoing epidemiologic investigations usually have not been provided with sufficient funds to ship DNA samples to new collaborators and provide extensive data analyses of clinical phenotypes when the aims of these new studies deviate significantly from those envisioned in the original project design.

2. Clinical investigators often encounter major difficulties in initial feasibility studies on the relationship between genetic abnormalities and a particular human disease. It is often impossible to obtain grant support to examine a new hypothesis without extensive preliminary studies. The difficulty of obtaining funding to develop such preliminary data often serves as a major barrier to progress in the field.

3. The division of academic credit between investigators who have collected DNA samples with associated clinical phenotypes for a specific purpose and those seeking to examine a new hypothesis not envisioned by the original study can inhibit free exchange of materials and information. The scientists initially collecting samples with the associated

data sets understandably believe that their intellectual contributions to the original study design and efforts in obtaining materials and phenotypes need to be recognized, while those generating new hypotheses about a particular disease believe that their novel insights and new experimental information also need to be acknowledged. In fact, the active collaboration of both sets of investigators is often essential in evaluating the new hypothesis. These interests can become even more difficult to resolve when commercial interests are involved.

## SOLUTIONS

### Completed Studies

To ensure continuing access to epidemiological studies that have ceased, a small grant mechanism should be established for the maintenance of samples collected by such studies. Such an award, for up to $50,000 direct costs per year, would cover the cost of storage and maintenance of the associated data set in easily retrievable form, as well as shipping of samples to approved collaborators. Grantees would be expected to assemble information about the study, the samples available, the nature of the information available, and the purposes for which samples and information can be accessed without further consent from the subjects, for the proposed NHLBI Web site. Grantees would also be expected to keep this information current (that is, as samples are used, or immortalization of cells conducted, or genetic marker information becomes available, this should be added to the Web site). Initial competitive peer review would be followed by strict administrative review annually. Ideally, the grant would be an extended period (5-10 years) provided that the investigator continued to discharge the obligations. It is emphasized that this award is to be used only for studies that are no longer active or have no continuing funding. Review criteria for this grant would include (1) availability of high-quality DNA; (2) consistent phenotyping of high caliber in the population; (3) appropriate informed consent for genetic testing and resource sharing; and (4) an appropriate review process to select projects to receive the samples.

### Ongoing Studies

Collaborative grant supplements to ongoing, funded epidemiologic investigations should be encouraged that will cover the incremental cost of preparing and shipping samples and making the collected information available to new collaborators examining hypotheses significantly different from those envisioned in the original study design. The availability of such supplemental grants should be advertised to holders of epidemiologic investigation grants as well as in Program Announcements to the community at large. Due to the rapid pace of the field, an expedited review of about 5 or 6 months duration, from submission to funding, should be provided for these applications.

### Feasibility Studies

Funding mechanisms should be developed that can support collaborative studies between new investigators and existing epidemiologic studies to determine the feasibility of a new study protocol. Such grants should be targeted

primarily to relatively new laboratories that do not have adequate funds to conduct preliminary investigations. In many cases, well-established laboratories will possess the necessary resources to carry out preliminary studies without additional funding. Program Announcements should indicate to the community the availability of such grants. If the application meets the test of joint submission by the holders of the samples and the investigators initiating the study, it should receive an expedited review of about 2 months duration. This should be explicit in the Program Announcement.

**Collaboration**

For the above grant applications, the NHLBI should emphasize to prospective grantees that new investigations will be most favorably viewed when there is evidence of intellectual input from the holders of the study samples, and a Memorandum of Understanding (MOU) exists between the investigators regarding the collaboration. Such an MOU would likely discuss the roles of the investigators and would discuss the criteria for determining authorship of subsequent publications. While NHLBI cannot and should not legislate the criteria for determining authorship and credit, it is important for the collaborators to agree upon them in advance. The difficulties surrounding commercial rights to the samples, data, and genetic findings may be minimized by appropriate materials transfer agreements (MTAs) prior to the exchange of materials. In practice, institutions will often wish to develop or customize their own agreements, depending on the circumstances. The agreements will typically provide that transfer of the material alone does not confer ownership of the material, and gives the recipient the right to work with the materials, but not to sell them or pass them on without prior approval. We believe that these provisions are reasonable.

**RECOMMENDATIONS**

3.1 *Completed studies.* Utilize small-grant mechanisms, with expedited review, to support the maintenance and distribution of DNA samples and accessing of associated data sets obtained by epidemiologic investigations after completion of such studies.

3.2 *Ongoing studies.* Set up a supplemental grant program, with expedited review, to support preparation and shipment of samples to new investigators.

3.3 *Collaboration.* Develop a small pilot grant program, with expedited review, to support collaborative feasibility studies between NHLBI-funded epidemiological studies and new investigators for the analyses of collected information directed at examining hypotheses significantly different from those envisioned by the original study design.

3.4 For all of the above grant applications, the NHLBI should emphasize to prospective grantees that new investigations will be most favorably viewed when there is evidence of intellectual input from the holders of the study samples and a memorandum of understanding exists between the investigators regarding the collaboration.

# PROTECTING HUMAN SUBJECTS

## INTRODUCTION

Informed consent provides the ethical foundation for all research involving human subjects, including research that utilizes tissue from human subjects. Informed consent for genetic research on stored tissue specimens (including whole 7blood cells or extracted DNA) presents several complex dilemmas, some of which differ for studies where specimens are already collected (retrospective) versus studies where specimens are not yet collected (prospective).

The public has already invested significant resources in collection of tissue specimens funded by the NHLBI, and the existing array of materials potentially suitable for genetic research is considerable. Major benefits to individuals and the public may result from research on these specimens, and further expense to the public may be minimized by promoting research on specimens that have already been collected. Even though some specimens may have been collected before the possibilities of genetic research were envisaged, such research should not be categorically prohibited. Further, specimens collected for other purposes may be appropriately utilized for such research in some circumstances. Prospective collections are, in certain respects, more straightforward because documents for informing potential participants and obtaining their consent can be designed today to include more key issues. Specimens should be obtained with appropriate explanations to allow for maximal understanding by subjects of the potential research use of the specimen, and subjects should be given the opportunity to authorize broad use of the specimen with appropriate protections. This approach will result in the most cost-efficient use of public funds to further scientific discovery while providing protection for research participants.

In this document, we adopt the definitions used by the American Society of Human Genetics "Statement on Informed Consent for Genetic Research" (Am J Hum Genet 1996; 59:471-4): **anonymous** specimens were originally collected without identifiers and are impossible to link to their sources, **anonymized** specimens were initially identified but have been irreversibly stripped of all identifiers and are impossible to link to their source, **identifiable** specimens are unidentified for research purposes, but can be linked to their sources through the use of a code, and **identified** specimens are those to which identifiers are attached and made available to researchers.

## ISSUES

Policy should be based on the premise that major potential benefits to the public must be weighed carefully against risks to individuals who volunteer for studies. Just as epidemiological and clinical studies have demonstrated an increased risk or prevalence of disease (such as hypertension, diabetes, obesity, coronary artery disease, etc.) in certain

subpopulations, such as gender or ethnic groups, genetic studies may also pose this similar risk. Counterbalancing this risk are the benefits derived from this research, including additional research and resources for prevention, control, and treatment.

When weighing benefits versus risks for participants in studies, there is the potential for harms and wrongs. **Harms** occur when an individual is actually injured, whereas **wrongs** are violations of a legitimate moral claim. When research specimens are identified or identifiable, harm may result from a number of events including (1) genetic discrimination and (2) invasion of privacy by recontact and recruitment for more research participation if the individual had not previously agreed to being recontacted. Harm is less possible when linkage to identity is effectively severed. Some claim that anonymizing a specimen may bring harm to subjects by precluding the possibility of personal medical benefits arising from research discoveries. Others do not accept this assertion.

In contrast to harms, wrongs are more broadly defined and may result even in cases where specimens are completely anonymized. Specifically, genetic research on anonymized specimens may bring about wrongs to a particular cultural, ethnic, or racial group without bringing actual harm to any particular individual. Informed consent that is sensitive to issues unique to particular cultural and/or ethnic groups will decrease the potential for wrongs and harms in genetic research. A genetic research policy must remain sensitive to the potential for such undesirable outcomes and make a reasonable attempt to minimize this possibility.

Because many conditions and diseases of most interest to the NHLBI will be complex disorders where there will be many genes each contributing small effects, the identification of any one genetic finding will typically not have dramatic implications for the risk of disease in any one individual in such studies. The Panel agrees that restrictions on genetic research of complex chronic diseases should not be based solely on protection for the relatively rare instances in which a single allele dramatically alters an individual's risk of disease. Nevertheless, for such rare instances, mechanisms must be established to give subjects the option of receiving information when it is deemed likely to benefit them substantially.

**SOLUTIONS**

In circumstances where adequate specimens are already in storage, the public will benefit if genetic research on stored specimens is facilitated because NHLBI can avoid unnecessary delays and extra costs involved in collecting new specimens. In order to access stored tissue specimens for retrospective or prospective studies, investigators may need to choose between accepting anonymized specimens and obtaining a second informed consent. In some cases, investigators may be willing to accept limits to identifying data in exchange for facilitated access to specimens. In cases where identifying data are critical to the scientific goal of the research, investigators must obtain Institutional Review Board (IRB) approval for the protection of the subject.

In judging the adequacy of a previous informed consent when an application is received to do new genetic research, several issues should be considered by IRBs and funding agencies: (1) the nature of the disease proposed for study, (2) the likelihood that knowing results of the research will harm or benefit an individual, (3) the availability of effective treatment or prevention for the disorder, and (4) the burden of such treatment. Decisions both about anonymizing a specimen and about the need for another consent must take into account answers to these questions.

Based on these considerations, the Panel proposes the following solutions:

1. **Ongoing and Completed Studies (Retrospective)**

   NHLBI should encourage the sharing of anonymous and anonymized specimens for studies broadly related to the goals described in the consent for the parent study. If this sharing is done with specimens that are anonymous or have already been anonymized, there is no obligation (and no possibility) to recontact subjects to obtain a second consent. Specimens provided anonymously cannot be traced back to any individual.

   When a new study needs access to identifiers, either because additional information is needed from the participants because results from the new study may suggest the necessity of recontacting participants, or because the research does not meet the definition of broadly related science, the protocol and a detailed plan for recontact must be reviewed and approved by the appropriate IRB. In cases where these issues are not clear, investigators should consult with the IRB. The Panel encourages the Office of Protection from Research Risks at NIH to develop guidelines so that IRBs will take consistent positions when consulted on this matter.

   No specimen, even if anonymous or anonymized, can be used in future studies (i) if doing so would violate conditions imposed by the original informed consent document (unless a new consent can be obtained); or (ii) without IRB approval if the new study is not broadly related to the goals of the original study.

   NHLBI should establish a facilitator function for the valuable resource of stored specimens. Similar to other valuable collections, the facilitator will maintain organization and control access to utilization. The facilitator function should be carried out by an Advisory Board, including some of the original investigators who collected the specimens, genetic researchers similar to those who will request specimens, and the public. Specifically, this NHLBI Advisory Board must attend to informed consent issues, carefully reading previous consent documents and considering their applicability to current requests, based on the guidelines set forth above. To enhance public accountability, the Advisory Board and investigator(s) should seek advice about consent issues from members of the group whose tissue will be studied.

**2. New Studies (Prospective)**

Informed consent should be obtained for these studies in a manner that will facilitate future genetic studies and other collaborative studies. Specifically, there should be a layered approach to informed consent.

a. In the body of the main consent form, subjects should be given the opportunity to consent separately (1) to participate in the current study, including genetics; (2) to store their specimens for the same uses; (3) to be recontacted; (4) to share their specimens with collaborating investigators involved in the current study; (5) to anonymize the specimen for use in future studies related to the main study.

b. In the next section of the consent form, subjects should be given the opportunity to consent separately (1) to participate in the genetic research on broadly defined disease area(s) related to the main study; (2) to be recontacted by the investigators (a) to obtain more information from the participant and/or (b) to relate results from the new study; (3) to store, transfer, and use the participant's specimen in future studies broadly related to the main study (with current or collaborating investigators); and (4) to anonymize the specimen for use in future studies broadly related to the main study.

c. In the third section of the consent form, subjects should be given the opportunity to consent separately (1) to use identified or identifiable specimen in studies unrelated to the main study; (2) to recontact the participant to (a) obtain more information from the participant and/or (b) relate results from the new study; (3) to store, transfer, and use specimen in future studies unrelated to the main study (with current or future collaborating investigators); and (4) to anonymize the specimen for use in future studies unrelated to the main study.

Investigators should strive to enhance clarity in the consent process, to keep the consent document brief, and to make use of current and emerging data about informed consent.

The consent document should include the statement that participants understand that they may decline participation in research with direct commercial intent or with possible future direct commercial intent, and that they have no financial claim to the profits made from any discovery based on their tissue.

Funding decisions on proposed future studies should be conditional on consent mechanisms that address these issues. NHLBI should communicate to all grant applicants the importance of these issues in the review process.

**RECOMMENDATIONS**

4.1 NHLBI should remind investigators and grantees that, when an investigator wants access to identified or identifiable specimens from NHLBI-sponsored studies, study protocols need to be submitted to the IRB or IRBs whose review and approval are needed. Some IRBs may also wish to approve requests for release of anonymous or anonymized specimens as well, although this Panel notes that such uses pose fewer issues and approval may be straightforward in most cases.

4.2 All requests for release of specimens for which NHLBI is responsible (i.e., contract and Immortalization Service specimens) should be approved by a subcommittee of the Specimen Resource Advisory Board. This subcommittee may be the same subcommittee as outlined in Recommendation 2.3, with the additional task of attending to the informed consent issues addressed in this document for samples that are not immortalized. They may also have to prioritize requests if there is danger of the specimen being completely expended (see Ensuring Adequate DNA Resources). In addition, the NHLBI should encourage Institute-supported studies where investigators and their institutions are responsible for the study specimens to create their own Advisory Boards to deal with the issues addressed in this document.

4.3 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.

Examples of a layered Informed Consent document should be available from the NHLBI, upon request, and also posted on the NHLBI Web site.

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