A Review and Analysis of the Ethical, Legal, and Social Implications (ELSI) Research Programs at the National Institutes of Health and the Department of Energy

Final Report of the
ELSI Research Planning and Evaluation Group

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Executive Summary

The Ethical, Legal, and Social Implications (ELSI) Programs were established in 1990 at the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH) and in the Office of Biological and Environmental Research (OBER) at the Department of Energy (DOE). The shared mission of these programs is to identify, analyze, and address the ethical, legal and social implications of the Human Genome Project (HGP) at the same time that the basic scientific issues are being studied. In July 1997, NHGRI's National Advisory Council for Human Genome Research (NACHGR) and DOE's Biological and Environmental Research Advisory Committee (BERAC) established the ELSI Research Planning and Evaluation Group (ERPEG). ERPEG's mission was to review and analyze the portfolio of ELSI research grants at both NHGRI and DOE, to participate in the development of the ELSI component of the new five year plan for the HGP, and to prepare a report for submission to NACHGR and BERAC summarizing its findings and making recommendations.

After performing an initial analysis of the ELSI research grant portfolio, ERPEG developed five goals to guide the ELSI research programs over the next five years. These goals were designed both to emphasize areas of research of ongoing importance and to identify emerging issues that require additional attention. They were seen by ERPEG as a work in progress that should be continuously updated and expanded. Following the publication of the goals as part of the HGP five year plan in the October 1998 issue of *Science*, ERPEG continued its analysis of the ELSI portfolio. This document summarizes the findings of this extended analysis and provides recommendations for strengthening the ELSI research programs at NHGRI and DOE.[i]

Since 1990, the NHGRI ELSI research program has supported more than 190 research and education projects and the DOE program has supported more than ninety-five. Supplementing these funded projects have been more than twenty-five ELSI "program activities"--workshops, conferences and related events--initiated and coordinated by ELSI staff to help ensure that the findings of ELSI research are appropriately translated into clinical and research practices and health and public policies. All of these projects and program activities fall into four program areas: (1) privacy and fair use of genetic information; (2) clinical integration of genetic technologies; (3) ethical issues surrounding genetic research; and (4) education and resources.

The impact of some of the early projects funded by the ELSI research program was limited to identifying issues and stimulating discussion within the then- relatively new ELSI research community. More recent projects have built on this early work and are beginning to exert a measurable influence on health and public policy and clinical and research practices. For example, in the area of privacy and fair use, the DOE-funded Genetic Privacy Act has had a direct impact on legislative activity at the state level. In the clinical integration area, the development of genetic testing protocols and of guidance for health care providers regarding the follow-up care of those with identifiable genetic risk factors for cancer would almost certainly not have occurred (or would not have been as carefully thought through) without the collaborative efforts and impressive body of literature emanating from the Cancer Genetics

[i] *This report was presented to the National Advisory Council for Human Genome Research at their February 27, 2000 meeting.*

Studies Consortium, which NHGRI funded and facilitated. In the genetic research ethics area, fundamental shifts in the way the mainstream genetic research community has begun to view the ethical and legal status of stored tissue samples can be seen as a direct outgrowth of the workshop on this issue co-sponsored by NHGRI and CDC, which in turn could not have taken place without the preliminary research on these issues funded by both NHGRI and DOE. Although the overall impact of the education and resources portion of the ELSI research portfolio is more difficult to assess, it does appear that the funded education activities have heightened awareness of genetics and ELSI issues in a variety of audiences and have provided some promising first steps toward improving how health professionals understand and use genetic information. In addition, the NHGRI ELSI program has provided support for two important and widely used online resources: BIOETHICSLINE and GeneClinics.

Despite the overall strength of the ELSI research programs and their grant portfolios, there are some weaknesses. Specific content gaps exist in each of the portfolio's four program areas and there are a number of emerging issues–such as behavioral genetics, genetic enhancement techniques, and other emerging technologies (such as fetal cell sorting, pre-implantation genetic diagnosis, and the ability to test for adult onset disorders in children or even in the prenatal period)–that will require additional attention in the coming years.

In addition, there are a few areas in the portfolio as a whole that could be strengthened. For example, the ELSI portfolio has supported a large number of "empirical" and "applied" studies that employ standard clinical and survey research methodologies to address issues affecting clinical practice and public policies. While these approaches have been very successful and should be encouraged, the portfolio could be significantly enriched if these projects were supplemented by more studies that use "theoretical" or "analytical" approaches--such as legal, historical, or philosophical analyses--to examine these same issues in broader contexts. For instance, there is a need for additional studies (like those being solicited under the new RFA on the ELSI issues surrounding human genetic variation research issued by NHGRI in 1999) that examine the impact of genetic research and technologies more broadly on family systems or on specific populations or community groups.

There also is an under-representation of investigators from certain disciplines, such as economics, cultural and physical anthropology, and religious and moral philosophy. In addition, very few principal investigators of funded projects have been members of minority racial or ethnic communities.

To begin the process of addressing these issues, **the ELSI research programs at NIH and DOE should continue to support research and initiate program activities to achieve the goals set out in the five-year plan published in the October 1998 issue of *Science***. Ongoing developments in genome science will create new ELSI challenges, which in turn will create new opportunities for ELSI research. To ensure that the ELSI research programs retain their agility and remain flexible to address new issues and challenges as they arise, **some resources should continue to be devoted to staff-initiated projects that use special grant or contract mechanisms to address specific high priority issues.** In addition, while gene sequencing of humans and other organisms will continue to influence all aspects of biology, including reproduction, development, health and illness**, the ELSI research programs should remain**

focused on issues directly related to genetic and genomic science and its integration into clinical and non-clinical settings, and should not at this time pursue the study of broader topics (such as human cloning or stem-cell research).

To ensure that the ELSI research portfolio is well-balanced and to further enrich its highly successful applied research projects, **the ELSI research programs should encourage activities that employ new theoretical perspectives from outside the traditional community of ELSI researchers and that promote cross-fertilization between ELSI research and other areas of the social sciences, law, and the humanities.** In addition, **they should recruit ELSI investigators from a broader array of disciplines, such as economics, anthropology, and religious and moral philosophy, and should make efforts to ensure that individuals from diverse communities are well-represented in the development and implementation of all aspects of ELSI research.**[ii] It is important, however, that these recommendations are used to enhance the existing ELSI portfolio and that they do not diminish ELSI's ongoing commitment to fund high quality applied research in clinical and non-clinical settings.

There are aspects of the existing NHGRI application and review processes which may contribute to some of the weaknesses in the ELSI portfolio. For example, NHGRI's continued heavy reliance on the rigorous and lengthy R01 application format may contribute to the relatively small number of more theoretical studies or small exploratory clinical projects represented in its portfolio. **The ELSI research programs should make use of alternative grant mechanisms to encourage the involvement of more scholars whose work is not well suited to the regular research grant mechanism (for example, legal, theological, or philosophical analyses) and to encourage the development of smaller, preliminary or exploratory studies.** To address the review concerns, **a standing study section with expertise in the disciplines of the applicants should be appointed to review NHGRI ELSI research applications.** This would allow study section members to develop a collective memory and give them the opportunity to reach a common understanding of the interdisciplinary nature of the ELSI research programs.

In general, DOE's ELSI grant application and review processes are subject to more flexible guidelines than NHGRI's. As a result they are both more difficult to assess systematically and less prone to problems arising from restrictive and multilayered application and review procedures. However, while the flexibility of the DOE processes allows for the possibility of more streamlined review and funding decisions, it is very dependent on the time and ability of program staff.

Although NHGRI's ELSI research program now appears to be adequately staffed, the DOE program continues to be staffed by a single individual, who also is responsible for overseeing other DOE programs. Given the reliance of the DOE application and review processes on staff time and energy, **the DOE should expand the current staffing of its ELSI research program.**

[ii] *The NHGRI Council endorsed ERPEG's recommendations and specifically highlighted the importance of recruiting minority investigators to ELSI research. Council members recommended that the next ELSI advisory group should consider this a high priority issue and should develop detailed recommendations for the development and implementation of targeted recruitment strategies.*

The lack of an effective system for tracking grant products after a grant has been completed remains a concern. This inability to track grant products may have contributed to what appears to be a lack of productivity of a small number of ELSI projects. **The ELSI research program staff should explore mechanisms that would provide incentives for researchers to report all products that result from a grant–even those that are published several years after the period of the grant has expired–so that they can be tracked and disseminated more effectively.**

Over the years, the ELSI research programs have done an increasingly good job of ensuring that the findings of ELSI researchers are communicated beyond the ELSI research community to those involved in the basic genomic and genetic research enterprise. There are a growing number of genetic researchers who not only recognize the importance of these issues, but who are actively involved in ELSI research and policy discussions. To ensure that this trend continues, **the ELSI research programs should strengthen activities that promote communication and collaboration between basic genetics and genomics researchers and ELSI researchers**

The ELSI research programs appear to be having a substantial impact on other NIH Institutes and Centers, other programs within the DOE, and other federal agencies and research organizations. To ensure the continuation of such activities, **the ELSI research programs should intensify their efforts to involve other NIH institutes, other federal agencies, and programs in other countries in the initiation and support of ELSI research.**

Following the expiration of ERPEG's charter, NHGRI and DOE should establish an ongoing joint planning and evaluation group to ensure that their ELSI research programs continue to identify and address the most important implications of human genetic and genomic research. The mission of this advisory group should be to: (1) evaluate the ELSI programs' progress toward the goals set forth in the most recent five-year plan; (2) assess progress on the implementation of the recommendations contained in this report; (3) identify emerging issues or priority areas that may require additional attention in the ELSI research portfolio; and (4) identify administrative or staffing issues that may require additional attention. **If administrative and other concerns preclude the formation of a joint NHGRI/DOE body, mechanisms should be established to ensure that there is continued interaction and coordination between the two programs.**

In conclusion, while many areas of science have ethical, legal, and social implications, this is the first time that these implications have been acknowledged by the granting agencies in the form of a formal budget allocation or "set-aside". This allocation of research dollars, in and of itself, may have compelled many throughout the research community to think more critically about the implications of their research, and to recognize that ethical, legal, and social implications are intrinsically a part of their work.

In addition, the very existence today of something thought of, in a fairly broad range of circles, as an "ELSI community" of researchers is an unambiguous indication that the ELSI research programs have, in their first decade of operation, succeeded in establishing a new and vital field of research. The wide range of research and education projects the programs have supported, coupled with the growing number of program activities they have initiated, largely define the

"state of the art" in this area and are beginning to exert a measurable impact on clinical and research practices and health and public policies. The ELSI research programs have funded productive and innovative researchers whose projects have laid a strong foundation for the further exploration and continued resolution of the ethical, legal and social implications of human genetic research.

I. Introduction

A. The ELSI Research Programs at NHGRI and DOE

The planners of the U.S. Human Genome Project (HGP) recognized that the information to be gained from mapping and sequencing the human genome would have profound implications for individuals, families, and society. They realized that while this information would have the potential to improve human health and well being dramatically, it would also raise a number of complex ethical, legal and social issues.

To address these issues, in 1990, Ethical, Legal and Social Implications (ELSI) Programs were created at both the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH) and the Office of Biological and Environmental Research (OBER) at the Department of Energy (DOE). The mission of these programs was to identify, analyze and address the ethical, legal and social implications of human genome research at the same time that the basic scientific issues were being studied. In this way, it was hoped that problem areas could be identified and solutions developed before adverse effects occurred.

The ELSI initiatives at NHGRI and DOE were established as two separate but complementary programs responsible for funding and managing research grants and education projects at institutions across the U.S. and abroad. An NIH-DOE Joint ELSI Working Group, consisting of a small number of leading bioethicists, medical geneticists, sociologists, legal scholars and others, was also set up in order to provide expert advice and to strengthen the activities of both programs. Established in 1990, this Working Group continued to provide program guidance to the ELSI programs until 1997.

Since its inception, DOE's ELSI program has maintained a primary focus on funding research and education projects. NHGRI's ELSI program also has been focused primarily on funding research and education projects, but was expanded and enhanced in the mid-1990s with the creation of two complementary entities: the Office of Policy and Public Affairs (established in 1995) and an Intramural Office of Bioethics and Special Populations Research (established in 1996). The Office of Policy and Public Affairs was created to provide information and analysis on ELSI policy and legislative issues and to sponsor workshops and conferences to assist in the development and dissemination of policy options and recommendations. The Office of Bioethics and Special Populations Research was created to conduct independent ELSI research and to assist researchers in NHGRI's Division of Intramural Research (DIR) in identifying and addressing ethical issues arising from their research. The activities of these two offices have helped to ensure that the findings of ELSI research are translated into sound policy. However, the core of the ELSI programs at both NHGRI and DOE remains their extramural research and education grant programs. *Throughout this report, the term "ELSI research programs" refers to the component of the NHGRI program that is focused on extramural ELSI research grants and to its counterpart program at DOE.*

As integral components of the U.S. HGP, the ELSI research programs are supported with federal research funds. NHGRI has committed five percent of its annual HGP research budget to funding research on ELSI issues. DOE reserves three percent of its HGP funding for ELSI

activities. By the end of FY 1999, NHGRI had spent more than $58 million and DOE had spent approximately $18.2 million on ELSI research and education projects, resulting in total ELSI expenditures of more than $76 million (See **Appendix A** for Budget Tables).

While the programs at NHGRI and DOE are closely related and have collaborated in a number of projects over the years (including the joint support of the former ELSI Working Group) they are independent and operate within different administrative structures and under somewhat different, although related, program priorities based on the missions of their parent agencies. The ELSI research program at NHGRI has been focused primarily on clinical research and health care policy issues and on the education of health care providers, while DOE's program has primarily supported projects more broadly related to the privacy and fair use of personal genetic information in various settings and the education of the public, students and policymakers.

Despite their differences, the two programs share four overarching aims. Ultimately, the ELSI mission is to support research and education activities that provide the conceptual and empirical foundation for the accomplishment of these aims. Individual projects funded through the ELSI research programs can be identified as contributing to one or more of these aims. For this reason, throughout this report these aims are referred to as "program areas" and are used as an organizing framework for the review and analysis of the ELSI portfolio. The four program areas are:

> *1. Privacy and Fair Use. To ensure that genetic information is interpreted correctly and used appropriately, and that public policies developed to protect genetic privacy and to reduce the likelihood of genetic discrimination are informed by ELSI research. Activities in this area examine the meaning of genetic information and how to prevent its misinterpretation or misuse.*
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> *2. Clinical Integration. To ensure that genetic technologies and information are optimally integrated into clinical settings, and that health care policies reflect the knowledge gained from ELSI research. Activities in this area examine the impact of genetic testing on individuals, families and society with the aim of informing clinical practices and policies related to genetic testing and counseling.*
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> *3. Genetic Research. To ensure that genetic research is conducted in an ethically sound manner, and that research policies are informed by ELSI research and experience. Activities in this area focus on informed consent and other genetics research ethics issues related to the design, conduct, participation in and reporting of genetics research.*
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> *4. Education and Resources. To ensure that the public and health and other professionals are genetically literate and aware of ELSI issues related to genetic technologies and information. Activities in this area include the development of ELSI and genetic-based curricula, web-based educational activities, PBS television series, videos and CD-ROMs for a wide variety of audiences.*

B. The ELSI Research Planning and Evaluation Group (ERPEG)

In July 1997, in response to recommendations made by a twelve-person committee appointed by NHGRI and DOE to perform an evaluation of the ELSI Working Group and its relationship to the other components of the ELSI program, NHGRI's National Advisory Council for Human Genome Research (NACHGR) and the DOE's Biological and Environmental Research Advisory Committee (BERAC) established the ELSI Research Planning and Evaluation Group (ERPEG).[1] The ERPEG membership includes eight individuals selected for their expertise, experience and/or accomplishments in areas relevant to the ELSI research program. Dr. LeRoy Walters, Director of the Kennedy Institute of Ethics, Georgetown University, was asked to serve as the group's chair. (See **Appendix B** for Charter, Roster and Meeting Dates.)

ERPEG's mission was to review and analyze the portfolio of ELSI research and education grants at both NHGRI and DOE. ERPEG was also asked to participate in the development of the ELSI component of the new five year plan for the HGP. After performing an initial review and assessment of the ELSI research grant portfolio, ERPEG drafted five research goals to guide the ELSI research programs in meeting their aims over the next five years. These goals were designed both to emphasize and strengthen areas of research of ongoing importance and to address emerging issues.

In May 1998, the draft goals were presented for public comment at a meeting that included representatives from the ELSI and genetics research communities, consumer groups, and others. Based on the comments provided, ERPEG further refined its articulation of the goals. The goals in their final form were published in *Science* in October 1998 as part of the overall five-year plan for the HGP.[2] The five research goals (each of which also includes related education activities) are as follows.

1. *Examine the issues surrounding the completion of the human DNA sequence and the study of human genetic variation.*
2. *Examine issues raised by the integration of genetic technologies and information into health care and public health activities.*
3. *Examine issues raised by the integration of knowledge about genomics and gene-environment interactions into non-clinical settings.*
4. *Explore ways in which new genetic knowledge may interact with a variety of philosophical, theological, and ethical perspectives.*
5. *Explore how socioeconomic factors, gender, and concepts of race and ethnicity influence the use, understanding, and interpretation of genetic information, the utilization of genetic services, and the development of policy.*

These goals encompass many of the emerging issues and program gaps identified in this report and are discussed in greater detail in Section II.D. They are a work in progress that should be continuously updated and expanded to address new issues as they arise. Given the complexity of these goals, a list of examples of possible research questions and education projects that could be included within each goal area was developed and is provided in **Appendix C**.

After completing the five-year plan, ERPEG was asked to continue its analysis of the NHGRI and DOE ELSI grant portfolio and to prepare a report for submission to the NACHGR and BERAC summarizing its findings and making recommendations for strengthening the ELSI research programs. This document is intended to satisfy that requirement.

C. Overview of Methods and Approach

To facilitate the evaluation of the ELSI research grant portfolio, ERPEG first examined the various research projects and program activities falling under each program area to assess their contributions to the area and to identify topics that may require further attention. ERPEG next evaluated the portfolio as a whole, assessing: the productivity of the grants; the quality of the grant products; the overall balance of the portfolio; the adequacy of dissemination of the grant products; and the overall impact of the projects that have been supported. The results of this analysis are set out in Section II of this report.

ERPEG then turned to an evaluation of various other aspects of the ELSI research programs, assessing: the effectiveness of the current grant application processes; the effectiveness of the current review processes; the adequacy of staffing; long-term grant productivity and tracking; interactions with basic genome science researchers and with other programs and agencies; and future planning and evaluation. The results of this analysis are set out in Section III of this report.

Based on its review and analysis, ERPEG developed a series of recommendations to guide the ELSI programs as they enter the next century. A summary of these recommendations is set out in Section IV of this report.

II. The ELSI Research Grants Portfolio

Since 1990, the NHGRI ELSI research program has supported more than 190 and the DOE ELSI research program has supported more than ninety-five research and education projects and conferences. They have resulted in a combined total of approximately 625 peer reviewed journal articles, books, newsletters, web-sites, PBS series, radio broadcasts, museum exhibits, videos, and education curricula. Supported activities have ranged from relatively small historical, philosophical, and theoretical research projects and legal analyses of specific ELSI issues to large clinical studies designed to examine the efficacy of particular genetic testing or educational interventions. Research methodologies used have included randomized controlled clinical trials, surveys, focus groups, personal interviews, video and curriculum development, and legal, historical, and philosophical analyses, among others. Principal investigators have come from a variety of disciplines, including (but not limited to) philosophy, medical genetics, genetics research, medicine, nursing, behavioral sciences, anthropology, history, law, genetic counseling, education, and consumer advocacy.

Supplementing these funded projects have been more than twenty-five ELSI "program activities": workshops, conferences and related events initiated and coordinated by ELSI staff to help ensure that the findings of ELSI research are appropriately translated into clinical and research practice and health and public policies. In the program's early years, the ELSI Working

Group assumed a major role in attempting to bridge the gap between research and policy. More recently, responsibility for carrying out these program activities has rested with staff in the NHGRI and DOE ELSI research programs and in the NHGRI Office of Policy and Public Affairs, who often work in collaboration with outside research, consumer, and professional organizations. This has resulted in a large number of ELSI activities which, while not directly funded through the research grant program, have had great impact. (Lists of research, education and conference grants and related publications and products are available on the NHGRI and DOE ELSI homepages: http://www.nhgri.nih.gov:80/About_NHGRI/Der/Elsi/elsiabs.html and http://www.ornl.gov/hgmis/resource/elsiprog.html#grants.)

This Section of the report summarizes ERPEG's findings with respect to both the funded research projects and the program activities in each of the four ELSI program areas. Section II.A. describes the major accomplishments of the program in each individual program area. Section II.B. analyzes the overall impact of the portfolio. Section II.C. identifies a number of weaknesses in the portfolio. Section II.D. makes recommendations for enhancing the content of the portfolio.

A. Major Accomplishments by Program Area

The challenges inherent in any attempt to evaluate basic and applied research programs have been widely recognized.[3] These difficulties are compounded by certain features unique to the ELSI research program. The conceptual nature of many ELSI grants can make attempts to quantify their effects especially problematic. While particular publications can sometimes be identified as having furthered the level of scholarship in a given area, it often is difficult to show a direct correlation between the research performed by a single investigator and the actual implementation of major research, health or public policies.

Although a small number of the grants funded in the earliest years of the ELSI research programs produced few tangible work products, this may merely reflect the fact that grants for the funding of conferences and for "think-tank"-type conceptual research projects predominated the portfolio at that time. Moreover, even though the early exploratory projects were not always productive in a strictly measurable sense, they did help to begin dialogue on the relevant issues, and in so doing, established a foundation for scholarship upon which later ELSI projects have built. The sophistication of ELSI grant applications has improved dramatically over time, perhaps reflecting a greater understanding of the application and review processes within the community. As a consequence, many of the more recently funded projects have been highly productive and have begun to have a measurable impact on practice and policy.

This Section describes the major accomplishments that have resulted from the funded projects and related program activities in each of the four ELSI program areas. The listing of accomplishments highlighted here is by no means intended to be exhaustive, but is rather merely representative of the types of projects and activities that have contributed to the ELSI research programs' success.

In an attempt to quantify one aspect of the impact of ELSI products, ELSI research staff performed a citation search on the publications referenced in this report, using the online Web of Science Cited Reference Search engine. This search engine identifies peer reviewed journal

articles that have been cited in other peer reviewed journal articles. While this approach provides some useful information, it has significant limitations. First, the raw number of times an article has been cited in a peer reviewed journal reveals little about the quality of the publication or its actual impact on practice or policy. Second, because the search engine used can identify only peer reviewed journal articles cited in other peer reviewed journal articles, the results reflect no citations of the referenced articles that may appear in other places (such as in books, reports, or newspaper articles). Third, the number of citations in peer reviewed journals may be affected by many factors, such as the date of the article's publication, the distribution and size of the audience of the journal in which the article was published, and the level of public interest in the topic explored. Nevertheless, ERPEG decided that using the Web of Science Cited Reference Search engine as an adjunct to the rest of the portfolio analysis would provide at least a "snapshot" of the potential impact that various publications have had on the community of researchers who are examining ELSI issues (See **Appendix D** for a listing of some of the more frequently cited ELSI publications.)

1. Privacy and Fair Use

ELSI-funded research in the area of privacy and fair use has focused primarily on two areas: (1) the privacy and confidentiality of genetic information; and (2) the potential for employment, insurance, and other types of discrimination or stigmatization based on the misinterpretation or misuse of genetic information. Both the NHGRI and DOE ELSI research programs have been very active in this area. Through the end of FY 1999, DOE's program had funded fourteen research projects and eleven conferences and NHGRI's had funded forty research projects and eight conferences in this area.

Much of the work in this area, while fairly conceptual, has resulted in the development of policy recommendations, some of which have been published in formats that have made them readily accessible to lawmakers, health and research policymakers, and regulatory organizations. One project that was funded by DOE and that has had a particularly strong impact was the development of the draft "Genetic Privacy Act" by George Annas (Boston University-Annas).[4] While this document has not led to the enactment of federal genetic privacy legislation, it has provoked substantial dialogue and has helped stimulate much legislative activity at the state level.

A second project, funded by the NHGRI (Case Western Reserve-Murray) looked at the impact of the HGP on access to medicine, health care, health insurance, and the distribution of scarce medical resources, and published a series of recommendations.[5,6] Another NHGRI-funded project (University of Florida-Moseley) examined a range of genetic testing and screening techniques and analyzed the social and economic incentives and disincentives to their use. This work resulted in a number of articles detailing policy options and guidelines to regulate the use of genetic testing by insurance companies, the most notable of which appeared in 1993 in the *American Journal of Human Genetics*.[7]

Two other notable projects, both funded by DOE (Shriver Center-Natowicz; Shriver Center-Reilly) used legal analysis and survey methodologies to examine the issues surrounding genetic discrimination, genetic privacy legislation, and the attitudes of life insurance companies toward the use of genetic data. These studies resulted in the publication of several articles in the

American Journal of Human Genetics and other journals that have been frequently cited by other researchers.[8,9,10,11] A more recent project, funded by NHGRI (Wake Forest University School of Medicine-Hall), is using a qualitative, comparative, case study methodology to evaluate the effect of state and federal laws restricting health insurers' use of genetic test information. The data from this project resulted in a January 1999 article in the *North American Actuarial Journal* and a January 2000 article in the *American Journal of Human Genetics*.[12,13]

A number of program activities have also been initiated in the area of privacy and fair use. For example, ELSI staff, assisted by members of the former ELSI Working Group, worked extensively with the U.S. Equal Employment Opportunity Commission (EEOC) and more recently with a number of consumer groups (most notably the National Action Plan on Breast Cancer), to help strengthen protections against genetic discrimination in health insurance and in the workplace. These activities were instrumental in several accomplishments, most notably: (1) the publication in March 1995 of guidance from the EEOC clarifying that protection under the Americans With Disabilities Act (ADA) extends to individuals who may be discriminated against in employment based on genetic predispositions;[14] (2) the formation of a task force of legal, health, genetic and bioethics experts that published a widely disseminated report in 1993 on the issues surrounding genetic information and health insurance;[15] and (3) the 1995 publication in *Science*, followed by three later publications, of workshop recommendations designed to protect against the possible misuse of genetic information.[16,17,18,19]

As discussed in greater detail in Section II.C.1. of this report, the ELSI research programs have achieved less success with respect to their support of projects that systematically collect empirical data to document the actual extent of genetic discrimination and stigmatization experienced by those who have or are at risk for genetic disorders. However, several preliminary studies exploring this topic have been funded. The earliest publication resulting from such a study, written by Paul Billings et al. and published in March 1992 in the *American Journal of Human Genetics*,[20] garnered considerable attention when first written, and remains one of the most frequently cited journal articles resulting from ELSI-supported research (with 138 citations, according to the Web of Science Cited Reference Search engine).

Apart from the DOE-funded work by Billings, a few other primarily descriptive studies attempting to document instances of actual genetic discrimination have been funded. One such project, performed as part of the NHGRI-funded HuGEM project at Georgetown University, involved a survey by Virginia Lapham soliciting information on a select population's perceived experiences with genetic discrimination.[21] A more recent NHGRI-funded study (Johns Hopkins-Faden) has taken a more broad-based and systematic approach to collecting empirical data on the values, beliefs, and experiences of persons with genetic conditions (and their family members) regarding informational privacy and access to health insurance in the context of health care reform. The results of this survey are currently being analyzed but have not yet been published.

2. Clinical Integration

The main focus of ELSI-supported activities in the clinical integration area has been research designed to examine the impact of genetic technologies on individuals, families and society so that health policies and practices related to genetic testing, counseling, and other interventions

can be better informed. NHGRI's ELSI research program has devoted a substantial portion of its research resources to clinical integration research, having supported seventy research projects and five conferences through FY1999. While DOE's ELSI program has been much less active in the clinical integration area, DOE did co-fund with NHGRI a landmark study by the Institute of Medicine (IOM) (IOM-Bulger), *Assessing Genetic Risks*, which examined such issues as the availability of adequately trained personnel to deal with genetic technologies, laboratory testing and quality control issues, availability and access to genetic information, and the financing of genetic services. The report of this study, published in 1994, has been widely distributed and has been used in the development of policies guiding the provision of genetics services.[22] The DOE also co-funded with NHGRI a project looking at genetic screening and patient knowledge and practices in two contrasting communities (UC Berkeley-Duster), which resulted in a number of book chapters and journal articles.[23,24,25,26]

Following up on the IOM study, and in response to an identified need for further guidance in the area of genetic testing, the former NHGRI/DOE ELSI Working Group established a Task Force on Genetic Testing, chaired by Neil Holtzman and Michael Watson and supported in part through an NHGRI ELSI grant. This task force published a series of recommendations in 1997 regarding the development and delivery of safe and effective genetic tests.[27] These recommendations were instrumental in the formation of the Department of Health and Human Services' Secretary's Advisory Committee on Genetic Testing (SACGT), which is responsible for identifying policy issues raised by genetic testing and making policy and procedural recommendations to the Secretary on how such issues should be addressed.

The research funded in the clinical integration portion of NHGRI's ELSI portfolio has established "state-of-the-art" counseling and education tools for the integration of genetic technologies into clinical settings and has, in essence, built the foundation for all future research in this area. NHGRI-supported projects have explored a variety of issues, such as: knowledge of and attitudes toward genetic testing and genetic counseling; the level of interest in and rates of use of various genetic tests; alternative strategies to obtain informed consent and educate individuals and families about genetic testing; the psychosocial impact of having (or not having) a genetic test; and the impact of genetic information on health and illness more generally.

Much of the NHGRI-funded research in the clinical integration area has arisen out of two special initiatives. The first was a Request for Applications (RFA) released in 1991, which solicited applications to study issues surrounding genetic testing and counseling for the then- newly discovered gene and genetic mutations associated with cystic fibrosis (CF). The second was an RFA released in 1994 in anticipation of the discovery of a number of genes and genetic mutations associated with the development of cancer, which was aimed at stimulating the study of issues surrounding genetic testing and counseling for heritable breast, ovarian, and colon cancer risks.

To promote collaboration among the individual research projects funded as a result of these two initiatives, to reduce duplication of effort, and to promote synergy among the projects, NHGRI sponsored the formation of two research consortia: the Cystic Fibrosis Studies Consortium (CFSC) and the Cancer Genetics Studies Consortium (CGSC). Both consortia–particularly the

CGSC–have been highly successful, and have set a new standard for collaboration, communication, and cooperation among researchers.

For example, in April 1997, an NIH consensus development conference on genetic testing for CF was held, at which research data from the CFSC studies were examined and presentations were given by a number of experts in the field.[28] An independent consensus panel that was appointed by the NIH Office for Medical Applications of Research to review the data then issued a series of recommendations on the use of genetic testing for CF.[29] The release of these recommendations was followed by a joint effort by the NHGRI, the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Geneticists (ACMG) to develop clinical, laboratory, educational, and informed consent guidelines to ensure the safe and effective implementation of voluntary CF carrier testing in the general population.[30] These guidelines are expected to be available for distribution in the Spring of 2000.

The CGSC initially consisted of fifteen independent teams that began meeting annually in 1994. They were joined by five new projects in 1997 and 1998, resulting in an even greater impact in the clinical integration area. In addition to more than thirty individual peer reviewed articles published by the principal investigators, several consensus papers have been jointly produced by consortium members. For example, three papers on informed consent procedures for cancer genetic testing and on follow up recommendations for individuals with inherited predispositions to colon, breast, or ovarian cancer have been published in *JAMA*.[31,32,33] Each of these articles has been heavily cited; a search of the Web of Science Cited Reference Search engine revealed more than 142 citations alone to the consensus article written by Wylie Burke et al. regarding follow-up care for individuals with a genetic predisposition to breast cancer published in the March 26, 1997 issue of *JAMA*. A fourth joint paper regarding more general ethical, legal and health policy issues in cancer susceptibility testing was published in 1997 in the *Journal of Law, Medicine and Ethics*.[34] In April 1999, an entire issue of the journal *Cancer Epidemiology, Biomarkers, and Prevention* was devoted to cancer genetics, introducing this type of research to a whole new research community. This issue included nine new papers summarizing some of the initial results of the CGSC projects.[35,36,37,38,39,40,41,42,43,44,45]

In addition to sponsoring the CFCS and CGSC, the NHGRI ELSI research program cosponsored a 1997 workshop with the Centers for Disease Control and Prevention (CDC) to examine the clinical, ethical, legal and social implications of the discovery of the gene for hereditary hemochromatosis and the possibility of widespread population-based testing for that disease. The recommendations issued as a result of that workshop were published in *JAMA* in 1998.[46] They also were used to help shape a new five-year, $30 million research initiative designed to examine the relevant issues, which NHGRI's ELSI research program is cosponsoring with the National Heart, Lung and Blood Institute (NHLBI).

As further discussed in Sections II.C.1. and II.C.2. of this report, because so much of the NHGRI-funded research in the clinical integration area has been specifically focused on genetic testing for CF and cancer risks, studies that analyze the issues in broader cultural contexts are currently under-represented in the portfolio. However, at least one highly innovative project has been funded: a study by Stephen Post focused on genetic testing for Alzheimer disease. This NHGRI-funded research has resulted in a range of articles, including a paper in *JAMA* setting

out an ethical perspective on the clinical introduction of genetic testing for Alzheimer disease[47] and an article examining future scenarios for the prevention and delay of Alzheimer disease in high risk groups.[48]

3. Genetic Research

ELSI-supported activities in the area of genetic research, while varied, have tended to focus primarily on studies of issues surrounding the design of genetic research protocols and the informed consent process for genetic research. Through FY 1999, NHGRI's ELSI program had supported eighteen research projects and seven conferences in this area; DOE's program had funded nine research projects and fifteen workshops or conferences.

A particular focus of activity in this area has involved examining the unique informed consent issues involved in genetic research using stored tissue samples and the effectiveness of existing guidelines to protect the privacy and other interests of those from whom such samples were obtained. An early study funded by DOE (Shriver Center-Reilly) examined issues of genetic privacy in DNA banking and DNA data banking to learn how informational privacy and related issues were being handled, especially with respect to computer security. The results of that research, which also included a series of guidelines, were published in five widely cited articles.[49,50,51,52,53] Another project, funded by NHGRI (University of Iowa-Murray/Weir), collected information about the status of informed consent for genetic research using stored tissue samples. The project examined how the requirements of informed consent were being met and how the concept of informed consent might be expanded to fit the unique context of genetic research when banked tissue samples are being used. Recommendations resulting from this study were developed and disseminated in 1995 in a two-part article in the journal *IRB: A Review of Human Subjects Research*, a publication widely distributed to U.S. Institutional Review Boards (IRBs).[54]

Another project currently being co-funded by NHGRI and DOE (University of Pennsylvania–Merz) on the topic of informed consent involved the development of an informed consent process for donation of blood to a DNA research bank using a brief series of vignettes to prompt enhanced cognitive processing of the information on the consent form. This project has also resulted in a number of publications, most notably, a 1999 article published in *Science* on IRB review and consent.[55]

Another NHGRI-funded project in this area that has had a substantial impact (U of North Carolina-Churchill) examined the process of informed decision-making regarding gene therapies. This project reexamined the legal and ethical basis of informed consent reflected in the Belmont Report, giving special attention to the distinction between research and treatment in the gene therapy context. This project resulted in a number of very significant publications and in recommendations for ensuring more informed decision-making with respect to gene transfer protocols.[56,57,58]

Yet another project funded by NHGRI (University of Oklahoma-Foster) examined two Native American communities' decision-making processes for participation in genetics research, analyzing issues of collective decision-making and the extent to which communal authority may

be exerted over individual members. Three papers detailing the findings of this study have provided an empirical foundation for much of the current discussion in the research and ELSI communities of the issues surrounding community consent in Native American populations and issues surrounding group consent more broadly.[59,60,61]

A DOE-funded project in the genetic research area that has attracted substantial attention is Rebecca Eisenberg's seminal work on intellectual property issues in genomics (University of Michigan Law School-Eisenberg), which has resulted in several highly-regarded journal articles.[62,63,64,65,66,67] While the issues surrounding the ownership of genomic data are extremely complex and are far from being resolved, the analytical data generated by this project have provided a sound foundation for the future development of intellectual property policies.

ELSI program staff have also initiated a number of program activities in the area of genetic research ethics. For example, to begin the process of addressing concerns about informed consent and other issues in genetics research, the Office for Protection from Research Risks (OPRR) and the NHGRI ELSI program collaborated to convene a workshop in 1992 to develop guidance for IRBs that were increasingly being asked to approve protocols for pedigree studies, gene discovery studies, genetic testing studies, and gene therapy protocols. The deliberations of this group resulted in the publication of a chapter on human genetics research in the 1993 issue of OPRR's *IRB Guidebook*, which is distributed to IRBs all across the country.[68] This was the first time the *Guidebook* had provided guidance on human subjects protections specifically for genetics research.

In addition, in 1994, anticipating the growing concerns about the adequacy of informed consent and privacy protections for the use of stored tissues in genetic research, the CDC and NHGRI's ELSI program supported a meeting to explore these issues. Following intensive deliberations, recommendations were developed and published in an article written by Clayton et al. that appeared in the December 13, 1995 issue of *JAMA*.[69] While these recommendations were initially considered controversial and criticized as overly restrictive, many are now becoming the standard by which informed consent for stored tissue research is obtained, and the publication is one of the most often cited ELSI products (having been cited in other peer-reviewed journals eighty times). NHGRI and Public Responsibility in Medicine and Research (PRIM&R) also cosponsored a workshop in 1996 to inform IRB members about human subject protections specifically related to genetic research.

Finally, to address some of the more immediate human subjects concerns in large scale genome sequencing, DOE and NHGRI staff have worked closely with researchers to develop guidance for the collection and use of samples for genomic research.[70] This guidance is being used by the researchers funded by the U.S. HGP and is being used as a model for genomic research in other public and private sector settings, both in the U.S. and abroad. ELSI staff and the ELSI community of researchers also played a critical role in the development of ethically sound guidelines for the development of a single nucleotide polymorphism (SNP) resource that is currently being used by HGP-funded researchers engaged in genetic variation research. Both of these activities are important accomplishments, particularly since (as further discussed in Section III.E. of this report), the need exists for enhancing direct communication between ELSI experts and genome researchers with respect to ELSI issues.

4. Education and Resources

DOE's ELSI program has identified education of students and the general public as one of its highest priorities and has funded forty-six education projects since 1991. The focus of NHGRI's education portfolio has been largely on the development of clinical genetics and bioethics resources for health professionals; NHGRI has funded forty education grants and two resource projects.

To support the education of legal professionals and other policymakers, DOE has been supporting the Genetics Adjudication Resource Project (GARP) (The Einstein Institute for Science, Health & the Courts-Zweig), a multipurpose and multidisciplinary education project to help prepare the nation's courts to adjudicate genetics and ELSI-related issues effectively. Since 1997, the project has designed and implemented a unique judicial educational program, provided basic science and ELSI orientation to more than twelve hundred judges, and established the most thorough collection of genetics-related legal literature to date, covering case law and statutes in twenty subject areas. The GARP has also produced a hypothetical case library and workbooks for the use of judges.

DOE has also funded a number of genetics education projects for students at the high school and college levels. The most notable of the products resulting from these activities has been a journal article on the relevance of the HGP for high school biology students[71] and the electronic and paper-based curricula on the implications of the HGP for public policy, privacy, and perceptions of human behavior developed by the Biological Sciences Curriculum Study (BSCS).[72,73,74,75] These programs were pilot tested, revised and then distributed free of charge to more than 30,000 high school and college biology teachers across the U.S. and to many more internationally.

Another successful program, which has been funded by NHGRI, is a pilot college course on the implications of genetic research developed at Dartmouth College (Dartmouth College-Green). This project developed and pilot tested a multidisciplinary course for college students, which was supplemented by a summer seminar for faculty to introduce them to ELSI issues and provide them with the tools to develop similar programs at their home institutions. Of the eight pairs of teachers in the initial faculty seminar, all have gone on to develop and teach ELSI courses at their colleges. Based on their experiences, the developers of this program have redesigned the faculty seminar to make it more accessible to a wider audience from a broader and more diverse range of colleges and universities.

Projects designed for the education of the general public have included DOE's DNA Files project (SoundVision Productions–Scott), a series of nationally distributed public radio programs focusing on developments in genetic science. The series began broadcast on more than 140 stations in November 1998; the producers anticipate an ultimate carriage of approximately 200 stations. DOE has also funded a number of education efforts targeted toward specific communities, including a curriculum on ELSI issues geared for Spanish-speaking students and parents (California State U., LA-Jefferson/Sesma)[76] and a project by the Association for Retarded Citizens of the U.S. (ARC-Davis) on the HGP and mental retardation, which produced a series of reports and fact sheets.[77] In addition, both DOE and NHGRI have funded a number of award

winning Public Broadcasting programs on the HGP and related ELSI issues, including the 1993 broadcast of "Medicine at the Crossroads" (WNET, Lester)[78] and "The Secret of Life" (WGBH-Apsell, co-funded with NSF), and the 1997 broadcast of "A Question of Genes: Inherited Risks." (Chedd/Angier Productions-Schwerin, co-funded by DOE and Smith Kline Beecham).[79]

In the health professional arena, NHGRI's ELSI research program has funded several surveys primarily designed to assess that group's knowledge and needs with respect to basic genetics education. One project (Johns Hopkins-Holtzman) found that knowledge of genetics and genetic tests among physicians was increasing, but that deficiencies in knowledge still existed.[80] The study also revealed that primary care physicians were likely to be directive when providing genetic tests rather than merely providing options for patients.[81] A second project–a survey of practicing nurses (ANA-Scanlon)--revealed that nurses had limited education in genetics, but expressed interest in being educated in the field. The study further revealed that nurses were already providing care on a regular basis to persons with genetic disorders, despite a lack of confidence in their own level of knowledge.[82] A third study (Georgetown University-Lapham) produced similar findings with respect to health professionals in University Affiliated Programs (UAPs), who routinely deal with individuals with genetic disorders and their families.[83]

The results of these preliminary studies led to the designation of health professional education as a high priority area for the education and resources portion of the ELSI portfolio at NHGRI. This in turn led to the development of several targeted education programs. For example, the Georgetown survey of allied health professionals led to the development of a series of seminars, fact sheets and other materials to help educate consumers and health care professionals about genetics topics.[84] Another successful project has been a summer institute for nursing faculty (University of Cincinnati-Prows), which has educated nursing faculty from a number of schools of nursing, including minority institutions, and helped them develop and teach courses on genetics and ELSI issues for nursing students.[85] The investigators from this project are currently analyzing the findings from the project's evaluation component to determine how to strengthen and expand the program to other more widely available electronic media.

In addition to these funded projects, staff in the NHGRI Office of Policy and Public Affairs, together with the leadership of the American Medical Association (AMA) and the American Nurses Association (ANA), have organized the National Coalition for Health Professional Education in Genetics (NCHPEG). NCHPEG is a coalition of more than 100 diverse health professional organizations dedicated to the development and dissemination of high quality and uniform education strategies and materials for health professionals. This group, which recently received a grant from the Robert Wood Johnson Foundation, is poised to assess the effectiveness and utility of the curricula and educational interventions developed through ELSI and other research programs and to help ensure their dissemination.[86]

Two NHGRI-funded projects designed to provide resource materials to a wide range of audiences are the heavily-used BIOETHICSLINE[87] (Georgetown University-Walters), which provides online bibliographic information on bioethics literature, and GeneClinics[88] (University of Washington-Pagon) which provides both bibliographic and practical medical genetics information for ELSI researchers, health practitioners and the general public. In a one year period from September 1998 to September 1999, BIOETHICSLINE (which is now available free

of charge on the National Library of Medicine's search interface, Internet Grateful Med) was accessed by more than 69,000 users who performed close to 107,000 searches. In that same period, the number of "hits" on the GeneClinics website has increased almost ten fold, from an average of 75 per day, to an average of 550 to 750 each day. This would average out to a total of between 200,000 and 300,000 "hits" each year.

While there are a number of weaknesses in the education and resources portion of the ELSI research portfolio (see discussion in Section II.C.1. of this report), ELSI investigators have for the most part done a good job of targeting the materials they have produced to their intended audiences, taking into account the differing levels of complexity appropriate for each and also the differences in the purposes for which the information will be used. Many of the projects have incorporated substantial content in the basics of genetics and molecular biology, distilled at an appropriate level for the audience in question. As a result, and because of the broad knowledge base of many of the investigators involved in the projects, the scientific and ELSI content of a number of the education and resources grant products have been outstanding.

B. Overall Impact of the Portfolio

As earlier noted, a number of projects funded by the ELSI research programs in the programs' early years did not appear to have much immediate impact beyond stimulating discussion within the relatively new ELSI research community. However, this has not been true of more recent projects. For example, in the area of privacy and fair use, the DOE funded Genetic Privacy Act has had a direct impact on legislative activity at the state level. In the clinical integration area, the development of genetic testing protocols and of guidance for health care providers regarding the follow-up care of those with identifiable genetic risk factors for cancer would almost certainly not have occurred (or would not have been as carefully thought through) without the collaborative efforts and impressive body of literature emanating from the Cancer Genetics Studies Consortium, which NHGRI funded and facilitated. In the genetic research ethics area, fundamental shifts in the way the mainstream genetic research community has begun to view the ethical and legal status of stored tissue samples can be seen as a direct outgrowth of the workshop on this issue cosponsored by NHGRI and CDC, which in turn could not have taken place without the preliminary research on these issues funded by both NHGRI and DOE.

The overall impact of the education and resources portion of the ELSI research portfolio is more difficult to assess. Due primarily to the absence of summative evaluations incorporated into the education projects funded to date, it has been difficult to determine whether the knowledge base of the audiences targeted by the various projects actually improved as a result of the educational interventions involved. However, although there are few objective data that confirm this perception, it does appear that the funded education activities have at least heightened *awareness* of genetics and ELSI issues in a variety of audiences (such as pre-college students and the rather specialized category of judges) and have provided some promising first steps toward improving how health professionals understand and use genetic information. The overall impact of media-based projects–television and radio programs targeted at broad public audiences–is much less certain.

While the quality of the published ELSI grant products has been somewhat variable over the years, most of the published studies, especially in recent years, have been very well researched and clearly written. Indeed, if there is a "state of the art" for such a diverse field there is little doubt that the scholarship represented in the current ELSI grant portfolio not only reflects it, but also to a large extent defines it. Most of the research is being published in peer reviewed journals, some of them very prestigious and widely-read.

Although the extent of actual dissemination of grant products is difficult to judge, it appears that ELSI products, in most instances, are being adequately disseminated. The very fact that so many of the articles have appeared in widely-read journals provides at least some assurance that the articles are being made accessible. The large number of citations to many of these publications also suggests that the articles are actually being read. NHGRI's and DOE's web pages contain comprehensive listings of many of the grant products funded by their respective agencies, which further aids in dissemination. (http://www.nhgri.nih.gov:80/About_NHGRI/Der/Elsi/elsipub.html and http://www.ornl.gov/hgmis/resource/elsiprog.html#grants.)

While the sheer number of times an article has been cited in other peer-reviewed articles cannot alone provide an accurate indication of either the article's quality or the extent to which it has been disseminated, it is worth noting that (according to the Web of Science Cited Reference search engine) thirteen of the ELSI-funded publications mentioned in this report have been cited twenty-five times or more in peer-reviewed journals, and five have been cited seventy times or more. These include: the two CGSC consensus articles by Wylie Burke et al. on follow-up care for individuals with inherited predispositions to breast and colon cancer published in the March 26, 1997 and March 19, 1997 issues of *JAMA* (142 and seventy-five citations, respectively); the article by Paul Billings et al. on genetic discrimination published in March 1992 in the *American Journal of Human Genetics* (138 citations); the Clayton et al. paper on informed consent for research on stored tissue samples published in the December 13, 1995 issue of *JAMA* (eighty citations); and the Hudson et al. paper on genetic discrimination and health insurance published in the October 1995 issue of *Science* (seventy citations).

There can be little doubt that the ELSI research programs are having a substantial impact on public policy and on health, research, and education practices. In the decade since they were established, the ELSI research programs have demonstrated that it is possible to: (1) anticipate ELSI issues and develop mechanisms to analyze them in intellectually rigorous ways that help to inform health and public policy deliberations; (2) develop meaningful interactions between scholars in the social sciences, law, and the humanities and those in genetics and medicine; and (3) raise general awareness of ELSI issues, at least among certain targeted groups.

In many ways, the most profound impact of the ELSI research programs may be that the investigation of ELSI issues now has a level of legitimacy that it never had before. In the past, one typically had to make a case why such issues were important and required further study; now, one increasingly has to make a case why they are not. More and more, the question appears to be not *whether* ELSI issues ought to be considered alongside basic scientific questions, but rather why they are not being more aggressively studied. In this respect, a genuine paradigm shift in the relationship between science and ethics, law, and public policy may well be underway–at least in the field of genetics.

The opportunity for such a paradigm shift would not have been possible without the strong commitment of NHGRI and DOE to their ELSI research programs. While many areas of science have ethical, legal, and social implications, this is the first time that these implications have been acknowledged by the granting agencies in the form of a formal budget allocation or "set-aside". This allocation of research dollars, in and of itself, may have compelled many researchers to think more critically about the implications of their research, and to recognize that ethical, legal, and social implications are intrinsically a part of their work.

C. Weaknesses in the Portfolio

Despite the overall strength of the ELSI research portfolio, ERPEG identified a number of areas that would require additional attention. This section describes specific gaps in the content of the portfolio in each of the four program areas and outlines a few crosscutting weaknesses in all program areas.

1. Gaps in Portfolio Content in Each Program Area

In the area of privacy and fair use, the lack of well-designed empirical studies documenting the actual extent of genetic discrimination experienced by persons who have or are at risk for genetic disorders remains a concern. On the one hand, the 1992 *American Journal of Human Genetics* article by Paul Billings et al. on genetic discrimination generated considerable attention when written, and as already noted, it remains one of the most frequently cited journal articles resulting from ELSI-supported research. However, the methodology used in the Billings study has been criticized, and the large number of citations to the article may be reflective primarily of other factors, such as the article's early publication date, the controversial nature of the topic, and the fact that so little other data have been published on the topic. In addition, the study by Mark Hall evaluating the effect of state and federal laws restricting health insurers' use of genetic test information has generated some provocative conclusions on the use of this information by insurance companies. However, it has not provided hard data on the actual incidence of genetic discrimination in health insurance decisions. Although a few other empirical studies on this topic have been or are being funded, these have been primarily descriptive in nature, involving cross-sectional surveys.

The small amount of rigorous empirical work on genetic discrimination in the ELSI research portfolio may turn out primarily to be a consequence of the fact that there have been relatively few documented cases of genetic discrimination to date. Nevertheless, much more work needs to be pursued in this area before definitive conclusions can be drawn. In addition, more empirical work needs to be done regarding the experiences of consumers and the attitudes of the general public with respect to *stigmatization* based on genetic status.

A number of gaps can also be identified in the clinical integration portion of the portfolio. As earlier noted, the majority of NHGRI-funded research in this area has emanated from the release of RFAs on carrier testing for CF and on testing for breast, colon, and ovarian cancer risks. As a result, almost all of the focus in recent years has been on these diseases, with little attention given to research on the implications of genetic testing for other, equally important, conditions. On the one hand, the recommendations that have come out of the consortia associated with the CF and

cancer RFAs will likely have a substantial impact on the way genetic testing for other genetic disorders is integrated into clinical practice. In particular, the CGSC's recommendations regarding predictive testing for cancer are likely to serve as a model for predisposition testing for other genetically-influenced complex diseases. Nevertheless, different conditions inevitably will have slightly different ELSI implications, and there remains a need for research focusing on a wider range of disorders.

Although NHGRI has funded a small number of grants focused on genetic testing for diseases other than CF and cancer, essentially absent have been comparative studies that examine the ELSI implications of genetic testing for a range of disorders. Also largely missing have been studies that examine even broader societal ELSI issues that cut across all categories of genetic or genetically-influenced disease, such as the degree of access to and use of genetic services by specific socially or culturally defined populations. In addition, there are few studies that examine the ELSI implications associated with behavioral genetics, genetic enhancement techniques, and other emerging technologies (such as fetal cell sorting, pre-implantation genetic diagnosis, or the ability to test for adult onset disorders in children or even in the prenatal period).

A second weakness in the clinical integration portfolio is that almost all of the studies in this area have involved "applied" or "empirical" research methods; there have been few purely "analytical" or "theoretical" studies. The concrete and pragmatic orientation of the research in this area should be applauded, because it has clearly contributed to the studies' success in influencing actual clinical practice. Nevertheless, the portfolio could be substantially enriched if some of the applied studies in the clinical integration area were balanced with other studies that examine the relevant issues in a broader societal context. For instance, there is a need for more studies (like those being solicited under the new RFA on the ELSI issues surrounding human genetic variation research issued by NHGRI in 1999) that examine the impact of genetic research and technologies more broadly on family systems or on specific populations or community groups.

Although the genetic research portion of the ELSI portfolio has generally been quite well balanced, gaps exist in this area, as well. For example, one subject that has been largely overlooked in this area has been the impact of economic and commercial interests on genomic research and on the development of genetic tests. Other topics requiring additional attention include: the ethical problems involved in the design of genomic research studies; how cultural factors influence the way genetic and genomic researchers design and carry out their studies; and how the genetic research enterprise is shaping cultural perceptions of genetics. This latter issue was explored in a somewhat broader context in the NHGRI-funded project by Dorothy Nelkin (New York U-Nelkin) which resulted in a number of journal articles and the publication of the book, *The DNA Mystique: The Gene as a Cultural Icon.* [89] While some of these issues are currently being addressed in the new NHGRI ELSI genetic variation RFA, studies that examine these issues in all areas of genetic research are needed.

A number of deficiencies in the education and resources portion of the portfolio can also be identified. First, despite the considerable efforts summarized above in ELSI-related education, a lack of consensus remains regarding the basic question of what constitutes adequate knowledge of genetics. A major gap in the education and resources portfolio is the absence of studies that

examine such fundamental issues as what each audience (such as students, teachers, nurses, judges, the lay public) actually needs to *know* about ELSI. The relative absence of individuals with specialized expertise in public science literacy on the investigative teams of many of the funded education projects may have contributed to this deficiency.

Second, no research has been done to address other underlying basic education issues, such as how various audiences actually learn genome-related content most effectively. This deficiency again reflects the lack of involvement in the funded projects by persons with public science literacy expertise. It also reflects the failure of many education projects to build in adequate mechanisms for conducting formative evaluations (evaluations designed to provide feedback to investigators while the project is in progress, enabling them to modify their strategies if necessary).

Third, to date none of the education projects have incorporated adequate summative evaluations (evaluations conducted after the educational intervention has been completed, to determine whether the intervention actually improved the genetic "literacy" of the targeted audience). Although a number of projects have used surveys and pre- and post-tests in an attempt to assess the impact of their interventions, more intensive evaluations that make use of a broader array of evaluation techniques (such as focus groups and in-depth interviews) are needed. While effective summative evaluations tend to be quite expensive to conduct, and require the involvement of persons with specialized expertise in educational evaluation, without such evaluations, it is nearly impossible to assess the actual impact (if any) that the funded education projects have had.

Finally, the current education portfolio is decidedly skewed toward applied studies. The portfolio is largely product-based, in the sense that it has produced a large number of books, conferences, workshops, and educational resource materials. There are a few projects in the clinical integration portion of the larger ELSI portfolio (such as those related to screening and testing for CF) that have asked more conceptual questions relating to the types of knowledge that individuals need in order to make informed decisions about the use of genetic medicine. However, there is a need for much more basic research on the dimensions of scientific and genetic literacy if optimal balance in the education portion of the portfolio is to be achieved.

2. Trans- Program Area Weaknesses

Apart from the specific content gaps in each of the four ELSI research program areas identified above, an analysis of the ELSI research portfolio reveals some weaknesses that cut across all program areas.

NHGRI's ELSI research portfolio has been heavily weighted toward clinical integration research–a trend that appears to have accelerated in recent years due to the RFAs on CF carrier status testing and cancer susceptibility testing, which both resulted in a large number of funded applications. As earlier described, many of the studies in the clinical integration area–particularly those funded under the cancer genetics RFA–have involved first-rate investigators, and have led to the development of recommendations that have had a measurable impact on clinical practice. However, an unintended side-effect of the success of these tightly focused grants has been a skewing of the entire ELSI portfolio toward research projects that address specific and somewhat

narrowly focused questions and away from projects that focus more broadly on the interactions between genetic issues and other aspects of the health care environment or society at large. For example, ELSI investigators typically have not tackled such broad, crosscutting questions as: "Is it fair that employers should have to hire employees whose health care will cost a great deal, and is it fair to provide greater protection for those with genetic predispositions to ill health than for those whose predisposition is the result of being born poor or having parents who smoke?" or "Are there ways to talk about behavioral genetics that do not devolve almost immediately into genetic determinism?"

The relative absence from the ELSI research portfolio of studies that reflect this breadth of approach may partially derive from another weakness in the portfolio: the fact (noted earlier) that it is heavily slanted toward empirical (applied) rather than analytical (theoretical) research, and the corresponding under-representation of investigators from certain disciplines, such as economics, cultural and physical anthropology, and religious and moral philosophy. While some research topics (especially in the clinical integration area) do not lend themselves as easily to broad, theoretical studies, a need still exists for greater cross-fertilization among ELSI researchers and for more involvement in ELSI projects by persons in disciplines that have traditionally been under-represented in ELSI research. In this way, broader theoretical interests can be applied to specific ELSI questions and the findings of ELSI research can be brought to bear on other scientific and sociological, cultural, and ethical analyses.

Another weakness in the ELSI research portfolio is that very few principal investigators in the funded projects have been members of minority racial or ethnic communities. While ELSI research projects have made a sustained and largely successful effort to include members of diverse groups as research *participants,* less success has been achieved in ensuring that individuals from these groups are well-represented on the project teams. Even projects focused on minority populations generally have had majority principal investigators. While this is not unique to ELSI research, given the significant cultural and societal impact that genetic research and technologies may have on individuals and groups, it is important that the ELSI research programs strive for broader representation in the planning and implementation of their projects.

D. Recommendations for Enhancing the Portfolio

As was mentioned earlier, the five ELSI research goals that were published in the October 1998 issue of *Science*, were developed based on the review of the ELSI portfolio summarized above. They encompass many of the content gaps and emerging issues that were discussed in the previous section and encourage the use of methodologies that are underutilized in the current portfolio. To reiterate, the goals state that the ELSI research programs should:

1. Examine the issues surrounding the completion of the human DNA sequence and the study of human genetic variation.
2. Examine issues raised by the integration of genetic technologies and information into health care and public health activities.
3. Examine issues raised by the integration of knowledge about genomics and gene-environment interactions into non-clinical settings.
4. Explore ways in which new genetic knowledge may interact with a variety of philosophical, theological, and ethical perspectives.

5. Explore how socioeconomic factors, gender, and concepts of race and ethnicity influence the use, understanding, and interpretation of genetic information, the utilization of genetic services, and the development of policy.

Given the breadth and complexity of each of the goals, a list of examples of possible research questions and education projects that could be included within each goal area has also been developed. This list, which is provided in **Appendix C** and is also available on the NHGRI website (http://www.nhgri.nih.gov/98plan/elsi/), is currently being used by both the DOE and NHGRI in the development of new grant solicitations. The ELSI research programs should continue to support research and education projects and initiate program activities to achieve these goals.

Since the publication of the new ELSI research goals in October 1998, the timetable for the completion of the first human DNA sequence has been accelerated. A "rough draft" of the sequence is now expected to be ready by the Spring of 2000 and the "final draft" will be finished by 2003. This accelerated timetable will lead to an even more rapid proliferation of new ELSI issues than was anticipated when the goals were drafted. As the HGP begins to explore the scientific aspects of human sequence variation on a large scale, it will be critical for biomedical scientists, ELSI researchers, and educators to examine the ELSI implications of this development for individuals, families, and communities in an even more critical and refined manner. The RFA on the ethical, legal and social implications of genetic variation research recently released by NHGRI's ELSI research program represents a first important step toward an increased commitment to studying these issues.

Other future developments in genome science will create new ELSI challenges, which in turn will create new opportunities for ELSI research. The ELSI research programs should retain their agility and remain flexible to address new issues and challenges as they arise. To help ensure that this occurs and that ELSI research and education activities continue to address the aims of the programs effectively, some resources should continue to be devoted to staff-initiated projects that use special grant or contract mechanisms to address specific issues identified as having high program priority.

Of the content areas that have been identified as requiring additional attention, two, in particular, deserve special mention. First, as scientists learn more about the genetics of complex human traits, including behavioral traits, the need for research on the ELSI implications of behavioral genetics and genetic enhancement will become more urgent. The NHGRI project lead by Eric Juengst (Case Western-Juengst) that examines the issues surrounding genetic enhancement has been quite productive, but as genetic research and technologies continue to advance, more studies in this area will be needed.[90,91,92,93] Second, there is a growing need for more research on the ELSI implications associated with the complex commercial environment in which genome research is being conducted and in which genetic tests are being developed, including studies that examine the role of economic incentives, such as intellectual property rights, on the biotechnology and pharmaceutical industries and on academic research institutions.

While there is clearly room for expansion in the ELSI research agenda, especially in the above-identified areas, the ELSI research programs should not set an overly broad agenda, and should not be engaged simultaneously on so many different fronts that the fiscal and human resources

that have been devoted to their core mission become diluted. Although gene sequencing of humans and other organisms will continue to influence all aspects of biology, including reproduction, development, health and illness, the ELSI programs should remain focused on issues directly related to genetic and genomic science and its integration into clinical and non-clinical settings, and should not at this time pursue the study of more broadly focused topics (such as human cloning or stem-cell research). Such topics are currently being addressed by the National Bioethics Advisory Commission (NBAC) or other advisory bodies.

The ELSI research programs should also increase their efforts to *balance* the overall content of their research grant portfolios. On the one hand, this balance can to some extent be ensured so long as the focus of the portfolios at NHGRI and DOE remains somewhat complementary. On the other hand, the balance of the studies funded *within* each program area may need more careful attention. For example, as explained in detail in Sections II.A. and II.B. of this report, the clinical integration portion of NHGRI's portfolio (which in turn accounts for a large portion of the overall ELSI research portfolio) has in recent years been heavily focused on CF and cancer, and almost all of the funded projects have involved applied (empirical) research. The ELSI research programs should encourage activities that employ new theoretical perspectives from outside the ELSI community and that promote cross-fertilization between ELSI research and other areas of the social sciences, law, and the humanities. In addition, they should recruit ELSI investigators from a broader array of disciplines, such as economics, anthropology, and religious and moral philosophy. It is important, however, that these activities enhance the existing ELSI portfolio and do not diminish ELSI's ongoing commitment to fund high quality applied research in clinical and non-clinical settings. Finally, the ELSI research programs should make efforts to ensure that individuals from diverse communities are well-represented in the development and implementation of all ELSI research.

III. Other Aspects of the ELSI Research Programs

In addition to reviewing and analyzing the content of the ELSI research grant portfolio, ERPEG examined various other aspects of the way the ELSI research programs operate at both NHGRI and DOE. Although most aspects of the programs were found to be functioning effectively, several areas of concern were identified. This section of the report identifies those areas of concern and makes additional recommendations for ensuring the programs' continued success.

A. Application Process

The process used to solicit ELSI research grant applications at NHGRI differs markedly from that used at DOE and is in many ways less flexible. This lack of flexibility is driven in large part by the stringent grant policies and guidelines established by the U.S. Public Health Service (PHS) for use by each of its agencies. These guidelines require several levels of approval before a grant solicitation can be released and also set strict standards for the submission and review of applications.

In fact, NHGRI and DOE have different terms for the mechanisms they use to solicit applications. DOE uses a Request for Applications (RFA) mechanism, which is updated and re-released each year and has no set receipt date so that applications are accepted throughout the year. NHGRI

uses a standing Program Announcement (PA), which is updated and re-released every few years and has three set receipt dates each year. In addition, the application format for DOE is less restrictive and can be more easily tailored to the needs of the applicant. The format used by NHGRI permits little latitude. Currently, under the NHGRI ELSI PA, only those applications that use the standard research grant application form, PHS 398, will be accepted. While the NHGRI ELSI research program allows applicants to submit education (R25) grants and conference (R13) grants, it does not make use of alternative mechanisms such as the small grant (R03) program, which involves a shorter, more streamlined application process.

In addition to soliciting applications under its standing PA, NHGRI's ELSI research program has also on occasion used the PHS RFA mechanism. However, this mechanism, which is distinct from the DOE RFA mechanism, is employed only in those instances where applications are being sought on a relatively specific topic which has been identified as a high priority. The release of an RFA is typically a one-time event, and the period during which the RFA remains open for submissions is time-limited. In general, this process takes about one year from concept approval to the actual funding of applications. As earlier discussed in this report, NHGRI's ELSI research program has employed the RFA mechanism on three separate occasions in the past: once to solicit applications relating to the clinical integration of testing for CF carrier status, once to solicit applications relating to cancer susceptibility testing, and once (more recently) to solicit applications on ELSI issues arising from the study of human genetic variation.

In 1999, for the first time, the NHGRI ELSI research program cosponsored a Request for Proposals (RFP). This RFP was designed to solicit a set of applications for a large multi-center study designed to examine issues surrounding phenotypic and genotypic screening and testing for hereditary hemochromatosis. In contrast to RFAs, RFPs solicit proposals under a contract mechanism. This five year, more than $30 million project will result in the funding of a coordinating center, a central laboratory, and four to six field centers, all of which will participate in this effort. As this project continues, it will be important to evaluate whether the use of this mechanism is appropriate for answering ELSI related questions.

There are also concerns about specific aspects of the existing application process. As has been indicated, some of these concerns stem from NHGRI's reliance on the R01 research grant application mechanism. While the R01 format seems appropriate for large studies focused primarily on empirical data gathering and analysis, the high level of detail the application form requires makes the application process arduous. This may tend to discourage all but the most elaborate of projects and may inhibit the development of smaller preliminary or exploratory studies.

In addition, NHGRI's continued reliance on the R01 format may account for the very small number of more theoretical studies (such as studies involving purely legal, philosophical, theological, sociological, or economic analyses) represented in its portfolio, which in turn accounts for some of the weaknesses identified in this report. Such studies may involve only a sole investigator or a limited number of investigators (rather than a large investigative team) and may require only a relatively modest level of support. The format of the R01 application is very structured and requires a detailed budget justification. This undoubtedly discourages some highly innovative theoretical projects from ever coming to fruition, although the recent institution of the

more streamlined modular budget format may help to alleviate this problem. The R01 mechanism may also create incentives for some investigators to "pad" their applications–either to make their application "fit" the format or to make the application process itself seem worth the trouble.

To address these concerns, the ELSI research programs should make use of alternative grant mechanisms to encourage the involvement of more scholars whose work is not well suited to the regular research grant mechanism (for example, legal, theological, or philosophical analyses) and to encourage the development of smaller, preliminary or exploratory studies. One approach would be for NHGRI to consider devoting a portion of its ELSI budget to the small grant or R03 mechanism to make smaller grants available to deserving investigators. This would help encourage scholars who engage primarily in theoretical work to explore ELSI issues. It would also encourage exploratory projects that "think outside the box" of mainstream ELSI research. Investigators who apply for these grants should be limited to fifteen pages to describe their project and required to submit only a brief budget justification for less than $50,000 in direct costs per year. The R03 mechanism initially should be adopted on a trial basis with perhaps $200,000 to $300,000 set aside. This decision should be reviewed and modified based on the number and quality of applications submitted.

In general, DOE's ELSI grant application process is subject to more flexible guidelines than NHGRI's and is thus both more difficult to assess systematically and also less prone to problems arising from restrictive application procedures. As a result, most of the concerns identified here do not apply to the DOE process.

B. Review Process

The process used to review grant applications at NHGRI also differs in many ways from that used at DOE. Program staff at DOE coordinate the review of grants and have a substantial role in making funding decisions. In general when an application is received, it is reviewed by DOE program staff to ensure that it fits the program guidelines. It is then either sent out to three experts for review or, if there are several similar applications, an ad hoc review group is assembled by program staff to handle the review of the set of applications. One of the reviewers is asked to moderate the panel, and program staff attend, but do not actively participate in the review of individual grants. Based on these reviews, program staff works with the DOE Office of Science Selecting Official to make the final decisions regarding which grants will receive funding.

NHGRI has a more formal and multilayered process that was established by the PHS for the peer-review of medical research grant applications. Grants submitted under the standing ELSI PA undergo an initial screening for completeness by the NIH Center for Scientific Review (CSR), are further screened for responsiveness by the ELSI research program staff, and are then reviewed by a study section (review group), which is established independent of program staff by Scientific Review Administrators within CSR or by the NHGRI Office of Scientific Review (OSR). While NHGRI ELSI research program staff attend the review meetings, they do not participate in the review of proposals.

The second level of review of NHGRI ELSI applications is by the NACHGR. At this level the ELSI research program staff and the NHGRI Director are given guidance about whether the initial

scientific and technical merit review of each application was fair and appropriate. Further, the NACHGR makes recommendations about whether there are particular applications that should have higher or lower program priority based on their knowledge of program priorities and scientific gaps and needs. This information must be taken into consideration by NHGRI staff and the Director when funding decisions are made. Ultimately, it is the Director of the NHGRI who makes all final funding decisions.

Perceptions exist within the relevant communities of scholars that NHGRI's ELSI review process is inconsistent and insufficiently responsive to interdisciplinary projects and to the contributions of different disciplines. Although this concern may be endemic in all peer reviewed research, ELSI applications, over the years, have in fact consistently received lower scores than other types of NIH (or NHGRI) research applications.

One explanation for the fact that ELSI projects have not tended to fare as well in the review process is that such projects, by their nature, tend to be multi-disciplinary–a feature that creates special difficulties in the review process. For example, a single ELSI project may address issues in genetics, ethics, law, health care policy, and anthropology or sociology. Not only is the challenge of meeting the standards for excellence in all of these disciplines daunting for the principal investigators in these studies (who must have wide-ranging expertise and the ability to coordinate individuals and synthesize ideas from multiple disciplines), but it is daunting for members of the review group, who similarly may not be able individually to claim expertise in all relevant areas.

This problem may be exacerbated by the fact that all ELSI research applications currently are reviewed by an *ad hoc* study section that is reformulated by CSR from one review to the next (ELSI education and conference applications are reviewed by a standing study section coordinated by the NHGRI OSR and are not subject to these same concerns). This may result in inconsistency from review to review, depending on the group's composition. In addition, the ever-changing composition of the group may contribute to some of the above-identified interdisciplinary difficulties, because it becomes all the more difficult to develop either a strong group dynamic or a thorough understanding of the criteria for excellence among the various disciplines.

To address these concerns, a standing study section with expertise in the disciplines of the applicants should be appointed by CSR to review NHGRI ELSI research applications. This would allow study section members to develop a collective memory and give them the opportunity to reach a common understanding of the interdisciplinary nature of the ELSI program. Members should be recruited for their commitment to interdisciplinarity and intellectual rigor. In addition, the use of consultants or special experts as *ad hoc* members to evaluate some proposals should be encouraged.

The flexibility of the DOE review process allows for the possibility of more streamlined review and funding decisions. However, for this reason it is also very dependent on the time and energy of program staff. This is potentially problematic given the current under-staffing of the DOE ELSI program. (This is discussed further in the following section.)

C. Staffing

The staff of the NHGRI and DOE ELSI programs are capable, experienced and hard-working individuals who are devoted to ensuring the success of the ELSI enterprise. In fact, the manner in which the ELSI research program staff at both NHGRI and DOE have worked with applicants and grantees to focus and refine their proposals and follow through with grants to completion stands as a model for the way staff in all federal research programs ought to function.

Although NHGRI's ELSI research program was severely understaffed for a number of years, it now appears to be adequately staffed, particularly with the addition of a third program director in 1999. However, the DOE ELSI program continues to be staffed by a single individual, who also is responsible for overseeing two other DOE programs. This has limited DOE's ability to track the progress of its ELSI program adequately and to initiate and support planning and evaluation activities. In addition, given the reliance of the DOE application and review process on staff involvement and oversight, this under staffing is particularly problematic. For these reasons, the DOE should expand the current staffing of its ELSI program.

D. Long-term Grant Productivity and Tracking

In the first few years of the ELSI research program, an apparent lack of grant productivity was a major concern. As earlier explained, the low productivity of some of these early projects may have been largely attributable to the fact that many of the grants funded at that time were for the support of conferences or highly conceptual projects, from which a large number of publications were never realistically expected to emerge. The majority of more recently funded ELSI research projects have, however, been quite productive. For example, as earlier noted in this report, well over thirty publications by individual investigators, coupled with several consensus publications, resulted just from the grants funded under the cancer susceptibility testing RFA and the associated consortium.

Another factor that may contribute to the appearance of a lack of productivity among some grants is the absence of a system at either NHGRI or DOE to identify systematically and collect in one place all ELSI research products. The ability of staff to contact investigators to collect this information is inhibited not only by a lack of staff time and resources, but also by federal policies that place restrictions on when and how much information can be requested from grantees. Currently, the only formal mechanisms available for grantees to apprise ELSI program staff of products resulting from funded projects are the annual noncompeting continuation reports required of all grantees, the report of previous findings that is required as part of the competitive renewal application for those who seek to extend their grants beyond the initial award period, and the final reporting mechanism that must be submitted within a year of the end of the project period. Once a grant has expired, however, information on grant products becomes difficult to obtain. This is paradoxical because it is precisely at this time that the publication of findings and recommendations is most likely to occur.

ELSI research program staff at NHGRI and DOE should explore mechanisms that would provide incentives for researchers to report all products that result from a grant–even those that are

published several years after the period of the grant has expired–so that they can be tracked and disseminated more effectively.

E. Interactions with Basic Genome Science Researchers and with Other Programs and Agencies

Over the years, the ELSI research programs have done an increasingly good job of ensuring that the findings of ELSI researchers are communicated beyond the ELSI community to those involved in the basic genomic and genetic research enterprise. Particularly as the ELSI research programs have become more involved in exploring the issues surrounding genetic variation research and other emerging genetic technologies, genomic researchers have begun to view ELSI issues as an important component of their own work. In fact there are a growing number of genetic researchers who not only recognize the importance of these issues, but who have initiated or become directly involved in ELSI research and policy discussions. This cross-fertilization between the ELSI research community and basic scientists has resulted not only in more effective and culturally sensitive research practices, but also in ELSI research projects that are more closely tied to emerging scientific questions and technologies.

Nevertheless, there are some in the scientific community who remain indifferent or even hostile to ELSI research–a fact undoubtedly due in part to a lack of exposure to the ELSI research enterprise. For this reason, the ELSI research programs should strengthen activities that promote communication and collaboration between basic genetics and genomics researchers and ELSI researchers. Enhancing such communication will not only improve the dissemination of relevant ELSI research findings back to the scientific community, but it also will help to ensure that ELSI research continues to address the most critical issues in genomic and genetic research. The annual contractor and grantee workshops held by DOE, which bring together all of the ELSI, genetic and genomic researchers funded by DOE, are a good model for the kind of effort that should be enhanced and regularized across both the DOE and NHGRI ELSI research programs. For example, efforts should be made to increase the visibility of the work of ELSI researchers at the annual Cold Spring Harbor meeting on genome sequencing, which traditionally has been heavily oriented toward genome scientists and has not had a strongly-integrated ELSI "presence."

The ELSI research programs appear to be having some impact on other NIH Institutes and Centers, other programs within the DOE, and other Federal agencies and research organizations. For example, the NHGRI CF and cancer genetics studies consortiums have set a new standard for collaboration, communication and cooperation among researchers, and are currently being used as models by other NIH Institutes and Centers and in interagency activities. The CDC, the National Institute of Environmental and Health Science, the DOE Bioremediation Program, the Swedish Foundation for Strategic Research, and others have established ELSI programs as part of their research efforts. The NIH has also formed a Trans-NIH Bioethics Committee to address ELSI issues arising across the NIH and has released a NIH-wide program announcement to solicit applications designed to examine ethical issues in research involving human participants. In addition, as noted earlier in this report, in a recent initiative to examine the feasibility of population-based genetic screening for hereditary hemochromatosis, the second-largest NIH institute (NHLBI) has issued a request for proposals (in collaboration with NHGRI) to examine not only the epidemiological and technical issues associated with such screening, but also the

associated ELSI implications. To ensure the continuation of such activities, the ELSI research programs should intensify their efforts to involve other NIH institutes, other federal agencies, and programs in other countries in the initiation and support of ELSI research.

In particular, as genetic tests are developed for additional single-gene disorders, NIH institutes that focus specifically on those particular disorders (or on the organ systems most closely connected with those disorders) should be encouraged to undertake more of the burden of supporting applied clinical ELSI research on the implications of testing for those disorders. This may free up needed resources and allow NHGRI's ELSI research program to focus more of its attention on broader issues that cut across disease categories, such as screening for genetic risk factors for complex diseases, the clinical integration of germ-line gene therapy, and other emerging genetic technologies.

F. Future Planning and Evaluation

Following the expiration of ERPEG's charter, NHGRI and DOE should establish an ongoing joint planning and evaluation group to ensure that the ELSI research grant portfolio continues to identify and address the most important implications of human genetic and genomic research. The mission of this advisory group should be to: (1) evaluate the ELSI programs' progress toward the goals set forth in the most recent five-year plan; (2) assess progress on the implementation of the recommendations contained in this report; (3) identify emerging issues or priority areas that may require additional attention in the ELSI research portfolio; and (4) identify administrative or staffing issues that may require additional attention.

The group should meet one to two times per year and submit a written report every three years. In addition, this group should be responsible for helping to develop ELSI goals for the next five-year plan for the HGP.

This future planning and evaluation group should include 8-10 members who have collective expertise in a broad range of fields relevant to ELSI research and education activities. The mix of disciplines represented by the group members should, at a minimum, include bioethics, genetics, social sciences, law, and education. The group also should have representatives from diverse communities and include at least one member of the general public.

Members would serve for four-year terms with terms staggered so that half of the members would rotate off every other year. In the interest of continuity and to help ensure some institutional memory, the membership of the group should include at least one member from ERPEG.

This recommendation regarding the establishment of an ongoing joint planning and evaluation group raises the question of whether a single group should continue to oversee both NHGRI's and DOE's ELSI programs, or whether, alternatively, separate groups should be established for each program. On the one hand, given the differences in the organizational structures of the programs' two parent agencies, in their ELSI research budgets, in their application and review processes, and in the subject matter focus of their respective ELSI grant portfolios, an argument can be made that it would be ill-advised for a single group to continue to provide advice to both programs. On the other hand, without some type of unified advisory mechanism to ensure that the agendas of the

two programs remain complementary and integrated and avoid unnecessary duplication of efforts, the continued success of the overall ELSI research enterprise will be difficult to ensure.

For these reasons, it would be preferable for a single joint planning and evaluation group to be appointed for both the NHGRI and DOE programs. To help ensure effective two way communication between the group and the advisory council to each program's parent agency, the group should include one member who serves on NACHGR and one member who serves on BERAC. If administrative and other concerns preclude the formation of a joint NHGRI/DOE body, mechanisms should be established to ensure that there is continued interaction and coordination between the two programs. It will be crucial for there to be some overlap in the membership of the individual advisory groups at each agency. In addition, staff of both agencies should maintain a high level of communication to ensure that the current complementary nature of the two programs continues into the future.

IV. Summary of Recommendations

The following is a summary of the major recommendations made in this report:

The ELSI research programs at NIH and DOE should continue to support research and education projects and initiate program activities to achieve the goals set out in the five-year plan published in the October 1998 issue of Science.

Resources should continue to be devoted to staff-initiated projects that use special grant or contract mechanisms to address specific high priority issues

The ELSI research programs should remain focused on issues directly related to genetic and genomic science and its integration into clinical and non-clinical settings, and should not at this time pursue the study of broader topics (such as human cloning or stem-cell research).

The ELSI research programs should encourage activities that employ new theoretical perspectives from outside the traditional community of ELSI researchers and that promote cross-fertilization between ELSI research and other areas of the social sciences, law, and the humanities.

The ELSI research programs should recruit ELSI investigators from a broader array of disciplines, such as economics, anthropology, and religious and moral philosophy.

The ELSI research programs should make efforts to ensure that individuals from diverse communities are well-represented in the development and implementation of all aspects of ELSI research.

The ELSI research programs should make use of alternative grant mechanisms to encourage the involvement of more scholars whose work is not well suited to the regular research grant mechanism (for example, legal, theological, or philosophical analyses) and to encourage the development of smaller, preliminary or exploratory studies.

A standing study section with expertise in the disciplines of the applicants should be appointed to review NHGRI ELSI research applications.

The DOE should expand the current staffing of its ELSI program.

The ELSI research program staff should explore mechanisms that would provide incentives for researchers to report all products that result from a grant–even those that are published several years after the period of the grant has expired–so that they can be tracked and disseminated more effectively.

The ELSI research programs should strengthen activities that promote communication and collaboration between basic genetics and genomics researchers and ELSI researchers.

The ELSI research programs should intensify their efforts to involve other NIH institutes, other federal agencies, and programs in other countries in the initiation and support of ELSI research.

Following the expiration of ERPEG's charter, NHGRI and DOE should establish an ongoing joint planning and evaluation group to ensure that their ELSI research programs continue to identify and address the most important implications of human genetic and genomic research.

If administrative and other concerns preclude the formation of a joint NHGRI/DOE body, mechanisms should be established to ensure that there is continued interaction and coordination between the two programs.

V. Conclusion

The very existence today of something thought of, in a fairly broad range of circles, as an "ELSI community" of researchers is an unambiguous indication that the ELSI research programs have, in their first decade of operation, succeeded in establishing a new and vital field of research. The wide range of research and education projects the programs have supported, coupled with the growing number of program activities they have initiated, largely define the "state of the art" in this area and are beginning to exert a measurable impact on clinical practice and health, research, and public policies. The ELSI research programs have funded productive and innovative researchers whose projects have laid the theoretical and empirical foundation for each of the programs' four overarching aims. These aims–focused on the areas of privacy and fair use, clinical integration, genetic research, and education and resources–will continue to guide the direction of the ELSI research program in the future.

The five new goals for the programs, outlined in the October 1998 issue of *Science* and supplemented with the additional programmatic recommendations contained in this report, will present major challenges for the ELSI research programs as they move forward into the next century. However, so long as the programs remain agile and flexible in their shared research agenda and responsive to the advice of a carefully constituted joint planning and evaluation group, the future vitality and success of the ELSI research enterprise is assured.

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Appendices

Appendix A.1. NHGRI ELSI Research Funding

Fiscal Year	Expenditures in $ Millions
1990	1.5
1991	3.9
1992	5.1
1993	5.3
1994	5.1
1995	5.3
1996	6.2
1997	7.0
1998	8.3
1999	10.6
TOTAL	**58.3**

Appendix A.2. DOE ELSI Research Funding

Fiscal Year	Expenditures in $ Millions
1990	0
1991	1.4
1992	1.8
1993	1.9
1994	1.9
1995	2.1
1996	2.0
1997	2.3
1998	2.5
1999	2.6
TOTAL	**18.5**

Appendix B.1.

ELSI Research, Planning and Evaluation Group (ERPEG) Members

WALTERS, LeRoy B., Ph.D (Chair)
Director, Kennedy Institute of Ethics
Georgetown University
Washington, DC

CLAYTON, Ellen Wright, MD, JD
Associate Professor of Pediatrics and Law
Vanderbilt University
Nashville, Tennessee

FISHER, Nancy L., M.D., M.P.H.
Associate Medical Director
Regence BlueShield
Seattle, Washington

LERMAN, Caryn E., Ph.D.
Director, Cancer Genetics
Lombardi Cancer Center
Georgetown University Medical Center
Washington, D.C.

MCINERNEY, Joseph D., MA, MS
Director, Foundation for Genetics
Education and Counseling
Baltimore, Maryland

NEBO, Rev. William E., M.Div
Senior Pastor, First Presbyterian Church
Livermore, California

PRESS, Nancy, Ph.D.
Associate Professor
Oregon Health Sciences University
Portland, Oregon

VALLE, David, M.D.
Professor of Pediatrics
John Hopkins University
School of Medicine
Baltimore, MD 21205

NHGRI/DOE Staff

BOYER, Joy T.
ELSI Research Program Director
Education and Special Populations Research
National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland

DRELL, Daniel, Ph.D
ELSI Program Manager
Department of Energy
Germantown, Maryland

McEWEN, Jean E., J.D., Ph.D.
ELSI Research Program Director
Law and Social Policy
National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland

ROSE, Susan L., Ph.D.
Human Subjects Research Program Manager
Department of Energy
Germantown, Maryland

SAYLOR, Susan
Program Assistant
ELSI Research Program
National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland

THOMSON, Elizabeth J., RN, MS
ELSI Research Program Director
Clinical Genetics and Research Ethics
National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland

Appendix B.2.

ELSI Research, Planning and Evaluation Group

Meeting Dates

September 10, 1997

December 14 & 15, 1997

February 5 & 6, 1998

April 20 & 21, 1998

May 28 & 29, 1998 (Airlie House)

September 28 & 29, 1998

March 29, 1999

September 20 & 21, 1999

Appendix B.3.

ELSI Research Planning and Evaluation Group (ERPEG) Mission Statement

BACKGROUND

In April 1996, the National Human Genome Research Institute (NHGRI) and the Department of Energy (DOE) appointed a 12-person committee to perform an evaluation of the ELSI Working Group and its relationship to the other components of the ELSI program. After several months of intensive interviews and deliberations, on December 12, 1996 the Committee issued its final report which contained three recommendations for restructuring the ELSI Working Group.

The committee's first recommendation related specifically to the ELSI Research Program:

> *"The existing [ELSI] Working Group should be restructured and designated the ELSI Research Evaluation Committee, housed within [NHGRI] as an advisory committee to the Director and the Council and within DOE advisory to the HERAC [Health and Environmental Research Advisory Committee] and the Genome Project."*

At its May 1997 meeting, the National Advisory Council for Human Genome Research (NACHGR) endorsed this recommendation, and the ELSI Research, Planning, and Evaluation Group (ERPEG) was established in July of that year.

MISSION

The mission of the ERPEG is to provide NHGRI and OHER/DOE with expert guidance on matters relating to their extramural ELSI research portfolios. This mission is understood to include long range planning and evaluation activities.

Specifically, the ERPEG provides expertise on existing and new research methods or approaches for studying ELSI issues; suggests new topics, issues and priorities; provides input on the use of funding mechanisms; and proposes methods for obtaining input from the public, scientific and other communities about current and future research priorities, (including ways of disseminating information back to these communities).

ERPEG activities include the following.

1. Strategic Planning for the ELSI Research Programs. This involves:

- becoming familiar with previously and currently funded grants in the NHGRI and OHER/DOE ELSI research portfolios, program announcements, RFAs and the mechanisms used to fund these projects;
- obtaining input from the public, health professionals, the genomic and ELSI

communities, and others on future directions for the ELSI Research Program;
- preparing the ELSI component of the NHGRI and OHER/DOE five year plan that is expected to be published in the peer reviewed literature in October 1998; and
- developing a more comprehensive long-range planning document that expands on the goals of the ELSI Research Program and focuses on implementation strategies.

2. ELSI Research Portfolio Evaluation. ERPEG is responsible for assessing how and to what extent: (1) the current ELSI research, training, and education activities fit with the goals of the Human Genome Project (HGP) in general, and the ELSI Research Programs in particular; and (2) the programs are positioned to anticipate and respond to new issues and developments that arise as a result of the HGP. The evaluation function involves:

   - surveying the NHGRI and OHER/DOE ELSI research and education grants portfolios with the goal of completing an in-depth analysis of each priority research area;
   - providing periodic reports on the progress of the evaluation to NACHGR and OHER/DOE; and
   - preparing a document detailing the findings of the portfolio review/evaluation.

ADMINISTRATION AND STRUCTURE

ERPEG, which has been established as a working group of the NACHGR and HERAC/DOE, will function until January 2000, at which time the NACHGR and HERAC will review its goals and accomplishments. ERPEG will begin its evaluation in 1997 allowing it to engage in the strategic planning process that will result in the development of the ELSI component of the NHGRI/DOE five year plan in 1997 and 1998. Once this 5-year plan is completed, ERPEG will continue its analysis of the ELSI grants portfolio and prepare a detailed Planning and Evaluation Report. These written reports will be presented to the NACHGR and HERAC and will also be made available on the NHGRI and OHER/DOE home pages and disseminated through other media.

The ERPEG roster inludes nine individuals who have been selected for their expertise, experience and/or accomplishments in areas relevant to the ELSI Research Program. Dr. LeRoy Walters, Director of the Kennedy Institute of Ethics, Georgetown University, serves as the ERPEG chair.

Appendix C. New ELSI Research Goals

Ethical, Legal and Social Implications (ELSI) Research

Goals and Related Research Questions and Education Activities for the Next Five Years of the U.S. Human Genome Project

This document was prepared by the ELSI Research Planning and Evaluation Group (ERPEG) to illustrate more fully the breadth and complexity of the ELSI goals. Each goal statement is accompanied by examples of possible research questions and education activities. These examples are meant only to give a flavor of the possible issues to be addressed, and are not, in any sense, exhaustive or comprehensive.

4. Examine the issues surrounding the completion of the human DNA sequence and the study of human genetic variation.

   Examples of Research Questions and Education Activities:

   - What strategies should be used to balance the needs for privacy and safety of individuals and groups with the scientific goals of creating resources for DNA sequencing and human variation research? (*e.g. How should research participants be informed about the fact that they may not be able to remain anonymous given the availability of their DNA sequence?*)
   - Will the discovery of DNA polymorphisms influence current concepts of race and ethnicity? (*e.g. How will individuals and groups respond to potential challenges to or affirmations of their racial and/or ethnic self-identification, based on new genetic information?*)
   - What new concerns are being raised by the commercialization and patenting of DNA sequence information in the public, academic and private sectors? (*e.g. What are the implications of domestic and international policies for the ownership of DNA sequence information?*)
   - What are the most effective strategies for educating health professionals, policy makers, the media, students, and the public regarding the interpretation and use of information about genetic variation?

5. Examine issues raised by the integration of genetic technologies and information into health care and public health activities.

   Examples of Research Questions and Education Activities:

   - What are the clinical and societal implications of identifying common polymorphisms that predict disease susceptibility or resistance? (*e.g. Will genetic testing promote risky behavior in persons found to be genetically resistant to particular pathogens, such as HIV, or environmental hazards, such as cigarette smoke?*)
   - What are the potential risks and benefits of integrating genetic testing for complex diseases, behaviors, and other traits into health care? (*e.g. What are the individual and*

social implications of developing pharmacologic treatments that are tailored to patients' genotypes?)

- What are the most effective strategies for integrating genetic information and technologies into clinical settings in ways that help practitioners see health and disease in a genetic context and what will be the ethical, legal and social consequences of their increasing availability and use? (*e.g. How will individuals be benefited or harmed by the integration of genetic information into individual medical records, managed care organization records, and public health registries?*)
- Will the availability of genetic information influence provider practice, change patient behavior, reduce morbidity and mortality, and/or reduce health care costs?
- What factors influence: who develops and regulates new reproductive genetic technologies; which technologies are incorporated into medical practice; and which technologies are accepted or rejected by the public? (*e.g. What issues may arise as a result of the development and use of germ-line gene therapies? How might the availability of these therapies affect concepts of disability?*)
- What are the best strategies for educating health care providers, patients and the general public about the use of genetic information and technologies? (*e.g. What are the most effective mechanisms for educating providers, patients and the public about the uncertainties inherent in genetic risk information?*)

6. Examine issues raised by the integration of knowledge about genomics and gene-environment interactions into non-clinical settings.

   Examples of Research Questions and Education Activities:

   - What are appropriate and inappropriate uses of genetic testing in the employment setting? (*e.g. Are there conditions under which it might be ethical and/or legal to use genetic testing to identify those employees who may have a susceptibility to workplace hazards? What implications does the Americans with Disabilities Act have for such testing?*)
   - What issues emerge from the collection, storage and use of blood and other tissue samples, including collections by the military, civil and criminal justice systems, commercial entities, and federal and state public health agencies?
   - What are the implications of obtaining genetic information for use in adoption proceedings and establishment of child custody and child support?
   - What are the implications of potential commercial applications resulting from the availability of genetic information about individuals and groups? *(e.g. Should commercial companies have access to personal genetic data for targeted product marketing?*)
   - What are the potential uses and abuses of genetic information in educational settings? (*e.g. Is placement of students on the basis of genetic data any more or less beneficial or harmful than tracking on the basis of traditional categories or classifications?*)

7. Explore ways in which new genetic knowledge may interact with a variety of philosophical, theological, and ethical perspectives.
   Examples of Research Questions and Education Activities:

   - Will continuing research in molecular biology and functional genomics affect how

individuals and society view the relationship of humans to one another and to the rest of the living world? (*e.g. As new genetic technologies and information provide additional support for the central role of evolution in shaping the human species, how will society accommodate the challenges that this may pose to traditional religious and cultural views of humanity?*)

- What are the implications of behavioral genetics for traditional notions of personal, social and legal responsibility? (*e.g. What role will the discovery of putative genetic predispositions to violent behavior play in criminal prosecutions?*)
- What are the implications of genetic enhancement technologies for conceptions of humanity? (*e.g. What ethical or theological challenges might be posed by the ability to alter the genetic makeup of future generations?*)

8. Explore how socioeconomic factors, gender, and concepts of race and ethnicity influence the use and interpretation of genetic information, the utilization of genetic services, and the development of policy.

   Examples of Research Questions and Education Activities:

   - How are individual views about the value of genetic research, the importance of access to genetic services, and the meaning and relevance of genetic information affected by concepts of race and ethnicity and by socioeconomic factors and gender? (*e.g. How have past misuses of genetic science and information influenced perceptions of genetic research and services among individuals from diverse communities and groups?*)
   - How is the impact of genetic testing in clinical and non-clinical settings affected by gender, concepts of race and ethnicity, and other social or economic factors? (*e.g. Will particular communities and groups be more vulnerable to employment discrimination based on genotype?*)
   - In what ways are access to, and use of, genetic information and services affected by ethnicity, race, gender, or socioeconomic status?
   - What are the most effective strategies to ensure that genetic counseling and other genetic services are culturally sensitive and relevant?

Appendix D. Citation Search on Selected ELSI Publications

Citations (performed 1/5/2000)

142 Burke, W., G. Petersen, P. Lynch et al. "Recommendations for Follow-up Care of Individuals With an Inherited Predisposition to Cancer: II. BRCA1 and BRCA2." *JAMA*. 26 March 1997: 277(12); 997-1003.

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