The Ethical, Legal, and Social Implications Program of the National Human Genome Research Institute: Reflections on an Ongoing Experiment*

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Abstract

For more than 20 years, the Ethical, Legal, and Social Implications (ELSI) Program of the National Human Genome Research Institute has supported empirical and conceptual research to anticipate and address the ethical, legal, and social implications of genomics. As a component of the agency that funds much of the underlying science, the program has always been an experiment. The ever-expanding number of issues the program addresses and the relatively low level of commitment on the part of other funding agencies to support such research make setting priorities especially challenging. Program-supported studies have had a significant impact on the conduct of genomics research, the implementation of genomic medicine, and broader public policies. The program's influence is likely to grow as ELSI research, genomics research, and policy development activities become increasingly integrated. Achieving the benefits of increased integration while preserving the autonomy, objectivity, and intellectual independence of ELSI investigators presents ongoing challenges and new opportunities.

INTRODUCTION

ELSI Program: Ethical, Legal, and Social Implications Program

NIH: National Institutes of Health

NHGRI: National Human Genome Research Institute

The importance of the ethical, legal, and social dimensions of genetics and genomics research—acknowledged in the initial assessment of the plans for the Human Genome Project (110)—was given formal recognition in 1990 with the establishment of the Ethical, Legal, and Social Implications (ELSI) Program, a component of the extramural genomics research program of the National Institutes of Health (NIH). The program began, and in many ways continues, as an experiment. It was legislatively instantiated in the National Institutes of Health Revitalization Act of 1993, when Congress, in establishing the National Center for Human Genome Research [the predecessor to the National Human Genome Research Institute (NHGRI)], mandated that "not less than" 5% of the NIH Human Genome Project budget be set aside for research on the ethical, legal, and social implications of genomic science (Pub. L. 103-43, 107 Stat. 181, Sec. 1521). More than 20 years later, the need to pay close attention to such issues is almost universally appreciated, and the terms ELSI and ELSI research—coined initially simply as bureaucratic shorthand for a particular NIH funding program—have become staples in the lexicon of the genetics and genomics field.

The term ELSI is often used in an imprecise way, which occasionally creates confusion about what the NHGRI's ELSI Program is and is not. In its earliest years, the program had a broad and somewhat diffuse focus, which sometimes erroneously led to its being understood as having substantial responsibility for the development of policy solutions to the full range of complex ethical and societal issues raised by genomics research, including resolution of the problem of genomic literacy. As the program has evolved, however, its mission has become much more focused, and today it is fundamentally a research program. Although the studies it supports often help to inform the development of policies and of education and community outreach efforts, the direct support of these activities is beyond the program's purview.

For this reason, and to avoid perpetuating confusion that may still persist, this review uses the term ELSI narrowly, in keeping with the meaning originally intended, as an acronym for the extramural research program at the NHGRI that funds studies of ethical, legal, and social issues in genomics. As used in this review, the term ELSI should not be taken as shorthand for a broader, amorphously bounded set of activities, or even as shorthand for a precisely delineated academic or scholarly discipline. In addition, because of the way this review uses the term ELSI, it avoids use of the term ELSI issues, and where the terms ELSI research and ELSI investigators are used, they are intended solely as shorthand for the research or the investigators funded by the ELSI Program and should not be understood in any more general sense.

This review describes the background of the ELSI Program, provides an overview of the current program portfolio, outlines the major funding mechanisms and the peer review process used by the program, and describes the growing priority-setting challenges facing the program. The review also summarizes the impact the program has had on the conduct of genomics research, on the practice of genomic medicine, and on broader legal and societal policies. It concludes with a discussion of the increased interactions between genomics research and ELSI researchers that have occurred over the past several years and the benefits and risks associated with enhanced integration between the two fields.

ORGANIZATIONAL STRUCTURE AND OVERSIGHT OF THE ELSI PROGRAM

The ELSI Program is currently the only dedicated extramural bioethics research program at the NIH and is the largest US funder of research focused on ethical, legal, and social issues in genetics and genomics. The program's budget has grown from $1.57 million in fiscal year 1990 to

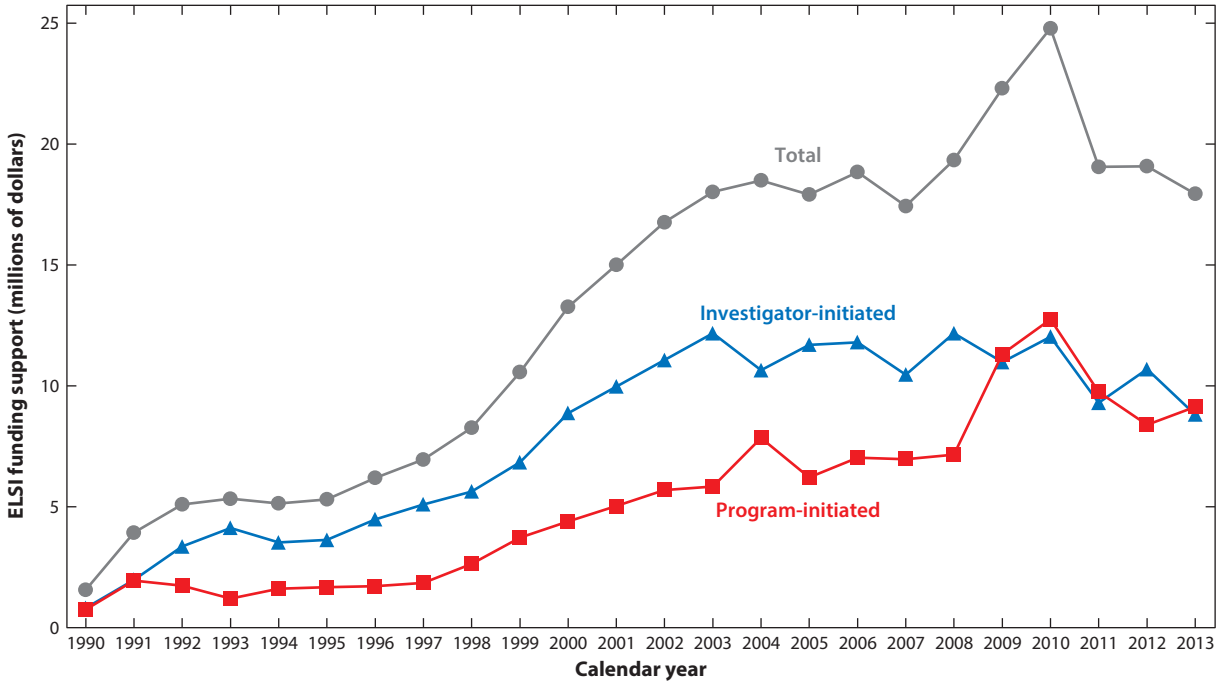

Figure 1

History of ELSI Program funding.

$18 million in fiscal year 2013 (**Figure 1**). Since its inception, the program has awarded almost $317 million in research support and has funded more than 480 projects (78); collectively, these have resulted in thousands of publications (77).

Administratively, at the NHGRI, the ELSI Program is housed within the Division of Genomics and Society. That division was established in 2012 to stimulate, enhance, and facilitate interactions between the ELSI Program and other components of the institute involved in related activities. These other components include two programs within the institute's Division of Intramural Research, the Social and Behavioral Research Branch (72) and the Bioethics Core (44) (both of which conduct independent research on similar issues), as well as the Division of Policy, Communications, and Education (70) (which does not support or conduct research but is involved in the development and analysis of policy options related to ethical, legal, and social issues in genomics and in education and community outreach activities) (**Figure 2**).

Over the years, the direction of the ELSI Program has been shaped by ongoing advice from the National Advisory Council for Human Genome Research (NACHGR) (79) as well as by a series of external evaluations, reviews, and NHGRI-wide strategic planning processes (**Figure 3**). In 2012, the NACHGR's Genomics and Society Working Group was established to make recommendations on short- and long-range planning and priority setting for NHGRI activities related to genomics and society—with primary emphasis on the ELSI Program (71).

NACHGR: National Advisory Council for Human Genome Research

OVERVIEW OF THE ELSI PROGRAM PORTFOLIO

The NHGRI maintains a searchable database of all grants the ELSI Program has funded since its inception (78) and of the major publications resulting from each grant (77). This database

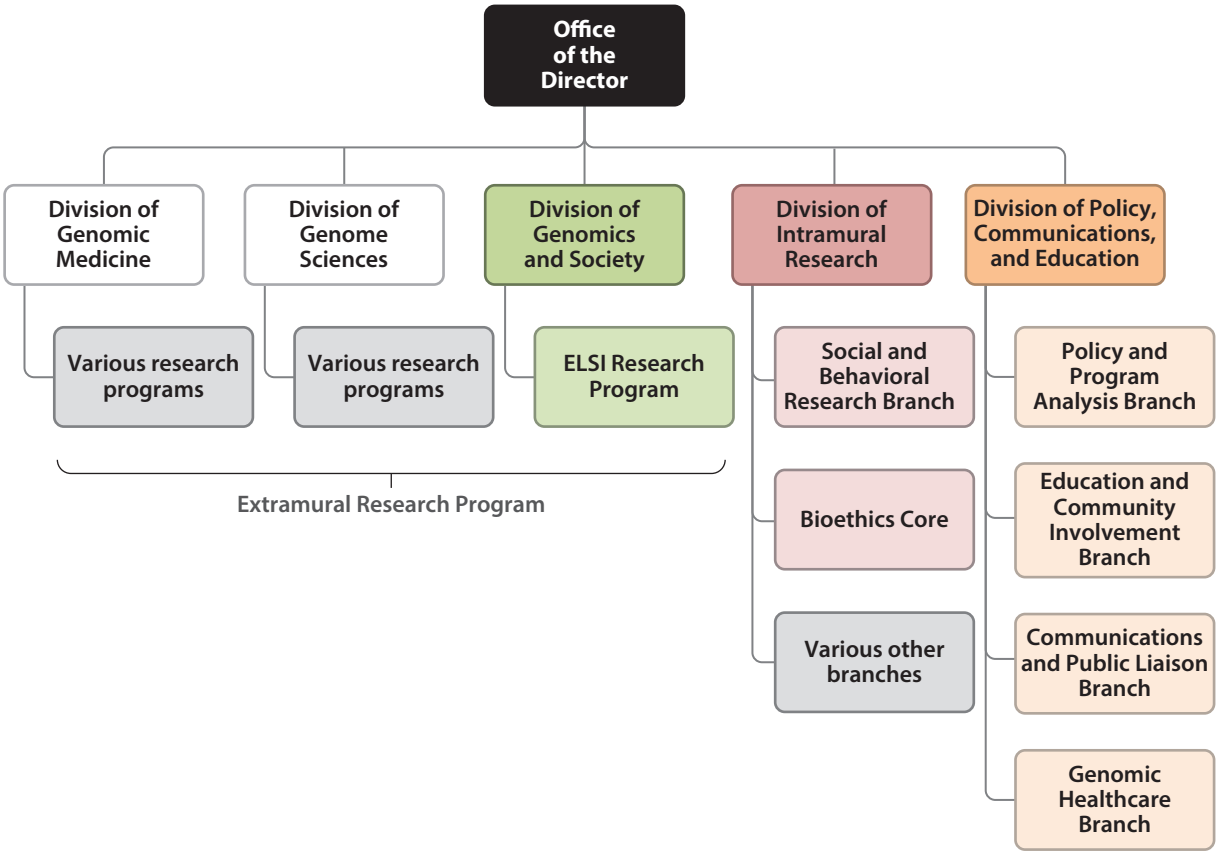

Figure 2

Organization of National Human Genome Research Institute (NHGRI) divisions relevant to the ELSI Program. The ELSI Program most commonly interacts with the NHGRI divisions shown in this figure. For more information on the full organization of the NHGRI, see Reference 80.

provides a reasonably comprehensive snapshot of the program's portfolio and its evolution over time.

A review of the database suggests that, although several of the topics that were being addressed two decades ago (e.g., informed consent, privacy, and issues related to the return of research and test results) are still being studied today, the topics are now being approached in more nuanced and methodologically complex ways. In addition, ELSI investigators have continually identified and addressed new issues [e.g., issues related to explorations of the human microbiome (62), genetic ancestry testing (56), and the growing impact of social media on the way genomic information is conceptualized and shared (57)]. Research results, initially often published as book chapters, are today increasingly published in high-impact, peer-reviewed clinical, genomics research, social science, and bioethics journals.

The program's current research priorities fall into four broad categories: psychosocial and ethical issues in genomics research, psychosocial and ethical issues in genomic medicine, legal and public policy issues, and broader societal issues (40) (**Figure 4**). Many funded projects encompass more than one category, and the categories themselves occasionally overlap (for example, the categories of genomic medicine and genomics research themselves raise legal and policy issues,

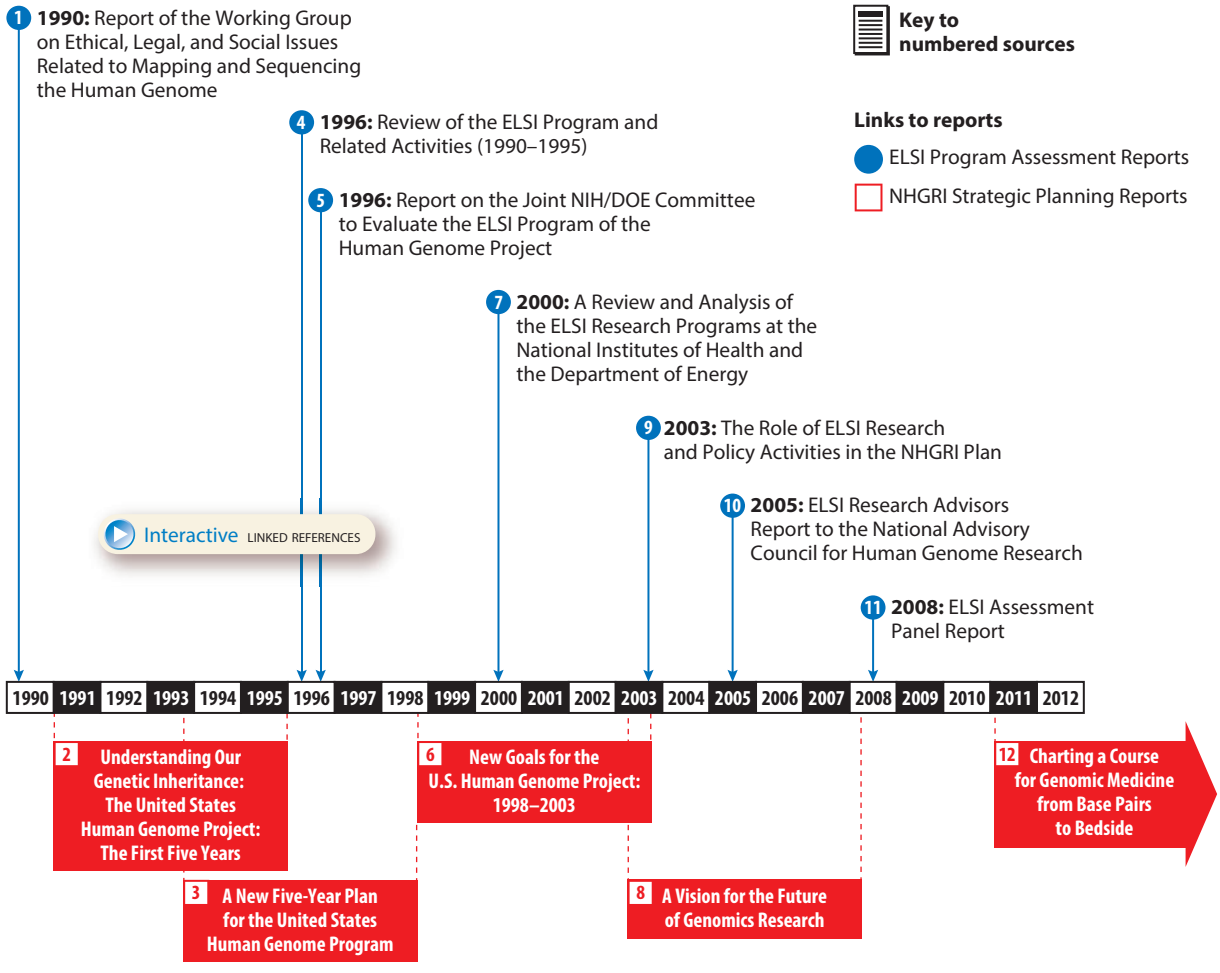

Figure 3

Reports shaping the course of the ELSI Program. In the online PDF of this article (available at **http://www.annualreviews.org**), click the titles to go directly to the associated sources.

and issues in both of these areas, as well as the broader societal implications of genomics, are often addressed through laws and policies). This makes it difficult to map precisely the percentage of the program's budget allocated to the support of research in each area. However, a rough analysis shows that approximately 40% of the current budget goes to studies of genomics research issues, 33% to studies of genomic medicine issues, 11% to studies of legal and policy issues, and 16% to studies of broader societal issues.

The program's research portfolio incorporates work by investigators from a broad range of disciplines, including (among others) genetics and genomics, clinical medicine, bioethics, the social sciences (e.g., psychology, sociology, anthropology, political science, and communication science), history, philosophy, literature, law, economics, health services, and public policy. Many of the individual grants are themselves highly multidisciplinary. Funded projects use a wide range of empirical (both quantitative and qualitative) and nonempirical methodologies. These range from experimental and quasi-experimental trials, surveys, structured and semistructured

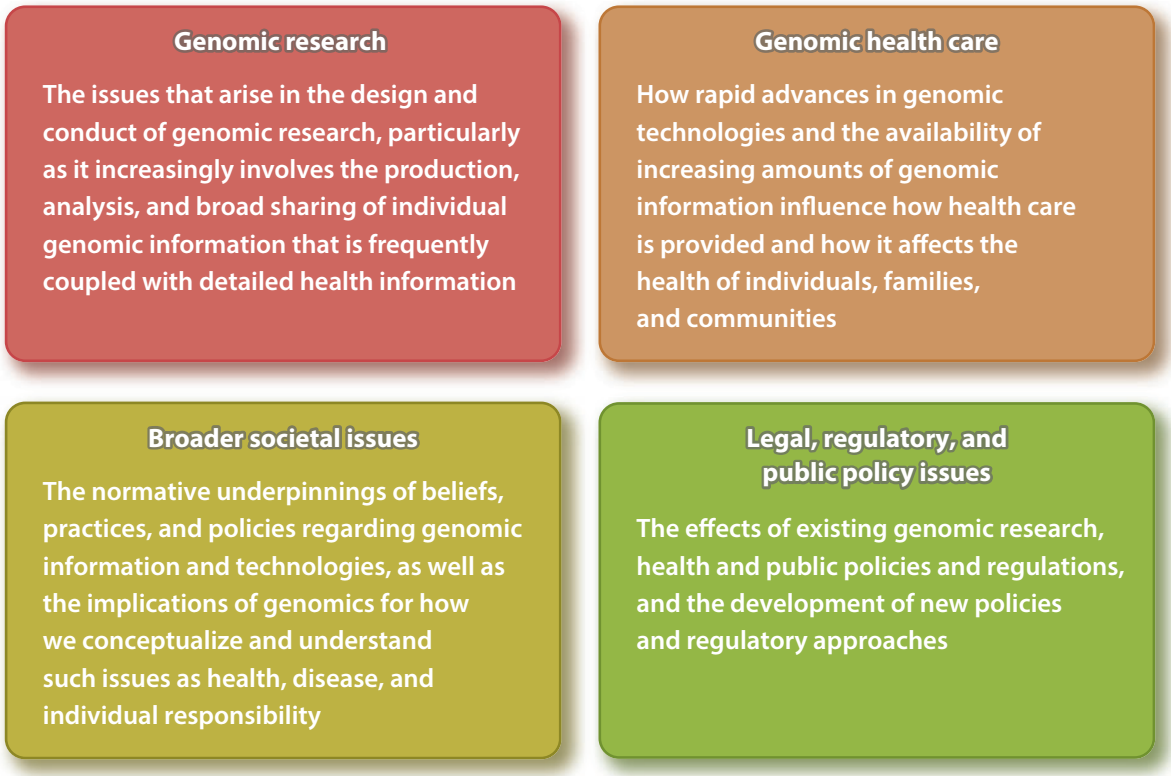

Figure 4

Current ELSI Program research priorities. For a more detailed discussion of each of these areas and a list of examples of possible research topics, see Reference 67.

interviews, and focus groups to ethnographic, legal, philosophical, archival, and oral history research. The program strives to maintain a balance between grants that utilize empirical and nonempirical methods, and nearly half the grants in the program's portfolio employ multiple methods.

Although the ratio of investigator-initiated to program-initiated research fluctuates from year to year, historically, most of the research funded by the program has been investigator-initiated (**Figure 1**). In large part, this reflects the program's desire to maintain the intellectual independence of its supported investigators. Such independence is arguably more important in this field than in many other areas of basic and clinical science because of the potential for studies focused on ethical, legal, and social issues to have direct policy implications.

MAJOR FUNDING MECHANISMS

PA: program announcement

The ELSI Program solicits investigator-initiated research applications through general program announcements (PAs) that contain broad statements of ongoing areas of programmatic interest. The program currently has three standing PAs for research grant applications: one for regular research grants (88), one for small research grants (90), and one for exploratory research grants (89). PAs are revised and reissued approximately every three years.

Program-initiated studies—studies of particular high-priority topics that are periodically identified as requiring immediate or more focused attention—are solicited through targeted requests for applications (RFAs) (for grants) or, less frequently, requests for proposals (RFPs) (for contracts) (**Figure 5**). When an RFA or RFP is issued, the program often establishes a consortium of those receiving funding, so that the supported investigators can address common issues, explore opportunities for synergy, and identify areas of consensus that can form the basis for policy recommendations with the potential for concrete impact.

Between 1990 and 2012, just over 40% of the program's budget was allocated to the support of RFAs or RFPs (**Figure 1**). Among these funded program-initiated projects are the Centers of Excellence in ELSI Research (CEERs). Begun in 2004 and now managed through a coordinating center, the CEER Program is designed primarily to support the creation and maintenance of the infrastructure necessary to foster highly transdisciplinary research; facilitate the translation of such research into health, research, and public policies and practices; and train the next generation of investigators in the field (68). Six center grants and three exploratory center grants (smaller grants to support the planning needed to develop a full center) are currently being funded (73). Full centers are funded for five years, with the possibility of one renewal for a second five years; exploratory centers receive three-year nonrenewable awards. Based on a recommendation of a prior working group of the NACHGR (27), the overall fraction of the ELSI Program budget allocated to the CEER Program has generally remained at less than one-third.

Apart from its regularly reissued PAs and periodically issued RFAs (including its support of the CEER Program), in recent years the ELSI Program has begun to contribute to the support of grants solicited through scientific initiatives issued by other NHGRI extramural programs that raise particular ethical, legal, or social issues and that, for this reason, need to include a defined ELSI research component (86, 87, 98, 102). The program also occasionally participates in relevant bioethics or social science initiatives issued centrally by the NIH or by other NIH institutes (81, 82, 94–97, 103–106). In addition, it has contributed a modest amount of funding to augment the support available for ELSI studies associated with a few genomics-related NIH Common Fund initiatives: the Genotype-Tissue Expression Project (**http://commonfund.nih.gov/GTEx**), Human Heredity and Health in Africa (**http://www.h3africa.org**), and the Human Microbiome Project (**http://commonfund.nih.gov/hmp**).

In addition to funding research, the ELSI Program supports research training activities and has been especially committed to training aimed at increasing the diversity of the investigators who conduct ELSI research. The program awards pre- and postdoctoral National Research Service Awards (83–85), administrative supplements to active research grants aimed at bringing a greater diversity of investigators into existing projects (101), grants for mentored research career development experiences (91), and grants for individuals who are transitioning to independent research positions (92). Currently, many of the supported training activities take place in the CEERs, which are required to include in their grant applications focused training plans, including plans aimed at increasing the diversity of trainees. By the end of 2012, the CEERs collectively had supported more than 100 postdoctoral, graduate, and junior faculty trainees, more than 25% of whom are members of groups traditionally underrepresented in ELSI research.

In its early years, in addition to supporting research and training grants, the ELSI Program funded a number of education projects. However, the program discontinued its education funding announcements in 2004; this decision was based on a recommendation of the external oversight group providing guidance to the program at that time (28) and on a growing recognition that, despite the clear need for enhanced public and professional education about genomic science and its implications, the ELSI Program was neither financially nor organizationally equipped to contribute meaningfully to the enhancement of genomic literacy among the public. Thus, for

RFA: request for applications

RFP: request for proposals

CEERs: Centers of Excellence in ELSI Research

Common Fund: a dedicated NIH funding program to support cross-cutting, trans-NIH initiatives that benefit from strategic planning and coordination

Genotype-Tissue Expression Project: an initiative to develop a resource for studying the relationship between genetic variation and gene expression

Human Heredity and Health in Africa: an initiative to support large-scale genetic studies and enhance research capacity in Africa

Human Microbiome Project: an initiative to characterize the genomes of microbial communities found in healthy and diseased individuals

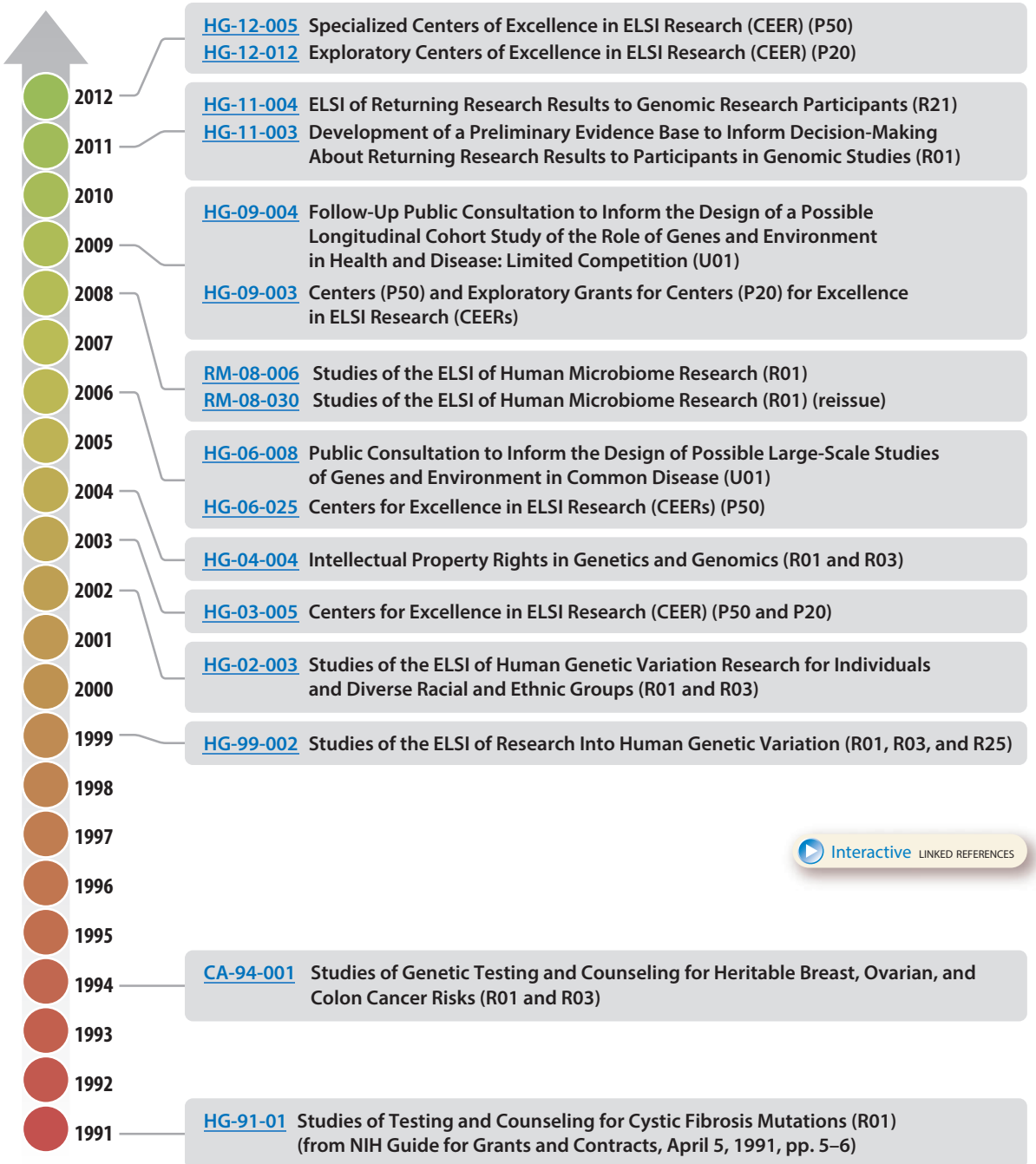

Figure 5

Requests for applications (RFAs) issued by the ELSI Program. In the online PDF of this article (available at **http://www.annualreviews.org**), click the RFA numbers to go directly to the associated webpages.

the past 10 years, funds that were earlier directed toward education projects have been redirected to research projects in areas where the funding is thought likely to make a greater impact. The NHGRI does continue to support a number of education resources and community outreach efforts, largely through the Education and Community Involvement Branch of the Division of Policy, Communications, and Education (75). In addition, the ELSI Program continues to fund a variety of meetings, workshops, and policy conferences, mainly through the freestanding NIH-wide conference grant mechanism (100).

PEER REVIEW

The locus of peer review of grants submitted to the ELSI Program (at least for most investigator-initiated research grants) has shifted over time among different sets of either ad hoc or standing study sections assembled at various times by the NIH Center for Scientific Review, the NHGRI, or both organizations jointly (29). Currently, the majority of investigator-initiated research grant applications are reviewed by the Societal and Ethical Implications of Research review group—a Center for Scientific Review–managed study section established in 2011 to handle the reviews of all investigator-initiated bioethics research grant applications submitted to ongoing or standing NIH-wide PAs (22). Applications submitted in response to program-initiated RFAs continue to be reviewed by ad hoc Special Emphasis Panels organized by the Scientific Review Branch within the NHGRI Division of Extramural Operations (formerly the NHGRI Office for Scientific Review) (69); these panels are composed of reviewers with expertise appropriate for the particular issues addressed by a given RFA.

The highly multidisciplinary nature of most ELSI research grant applications presents special review challenges because it is often difficult to identify reviewers with the expertise to cover every area of research included in the applications. The problem is exacerbated by the small size of the ELSI research community, which places many potential reviewers of ELSI research grant applications in conflict with one another. An additional challenge arises from the fact that many ELSI research applications are explicitly designed to anticipate the societal implications of particular genomic technologies in advance of their actual implementation, and for this reason, they often require investigators to design their studies in ways that involve asking questions largely in the abstract. However, such applications are sometimes criticized for being overly speculative or hypothetical. Applications that propose legal research or other primarily conceptual or normative methodologies can also present unique challenges because they do not lend themselves easily to the standard NIH grant application format. In addition, reviewers from more empirically oriented disciplines sometimes find it difficult to understand and appreciate legal and normative research methods. ELSI Program staff continually work with applicants so that they can anticipate, and try to meet, challenges of these kinds.

PRIORITY-SETTING CHALLENGES

In setting program priorities, the ELSI Program strives to maintain a balance between breadth and depth in the research portfolio while taking into account the broad range of stakeholder interests involved. The need for careful priority setting has been especially pronounced in recent years, in part because of the shift that is occurring in the field of genomics from an emphasis on basic research (research aimed at understanding the structure and biology of genomes and the biology of disease) toward an emphasis on research with identified human participants and immediate clinical applications. The latter type of research, by its nature, raises an expanded array of ethical issues, which the ELSI Program is increasingly being called upon to address.

Ironically, however, pressures on the program to spread its limited research dollars across a wider range of topic areas are occurring just as the NIH (and thus the NHGRI) is experiencing unprecedented budget cuts. With the ELSI Program's legislatively mandated 5% set-aside tied directly to the size of the overall NHGRI appropriation, a strain greater than ever before is being placed on limited program resources, which amplifies priority-setting challenges.

Exacerbating this situation is the fact that, although the NHGRI claims less than 2% of the total NIH budget (107) and all NIH institutes now conduct a substantial amount of genomics research, the NHGRI is the sole NIH institute with a dedicated budgetary set-aside for extramural bioethics research. A robust NIH-wide intramural program exists that addresses a range of general bioethical issues (30), but that program has no extramural funding counterpart (31); the Bioethics Core and the Social and Behavioral Research Branch at the NHGRI, likewise, are exclusively intramural programs. Several other NIH institutes sign on to the ELSI Program's PAs and occasionally fund or cofund grants focused on diseases related to their institutes' defined areas of interest. However, with the recent mounting of budgetary pressures across all of the NIH, the number of other institutes that participate actively has dropped.

This situation poses a dilemma for the ELSI Program about whether it should continue to fund certain categories of research. An example of such a category is disease-specific ELSI studies that could, and arguably should, be supported by the categorical NIH institutes whose mission it is to fund studies related to particular diseases (for example, studies of how genetic testing for breast or colon cancer susceptibility influences decision making regarding prophylactic mastectomy or colonoscopy). Funding disease-specific studies that are not aimed at the development of models with potentially broader applicability diverts scarce ELSI Program dollars from other, potentially more generalizable, studies and may also diminish the incentive for other institutes to support these types of studies themselves. At the same time, ceasing to fund such studies could result in some important disease-specific ELSI research lacking any home for funding and thus not being done at all. [Although some small, typically more conceptual, studies of ethical, legal, and social issues can be done without funding agency support (65), most of the larger, empirically oriented studies require it.]

Similar questions arise about whether the program should continue to fund research on issues arising from uses of genomic information in nonmedical contexts. Historically, a small portion of the program's budget has been allocated to the support of such research—e.g., studies addressing topics such as potential uses of genomic data in insurance, employment, education, criminal justice, family law, and the military (2, 4, 16, 21, 45, 112). On the one hand, some of the thorniest issues in the field arise from potential uses of genetic and genomic information in areas far removed from biomedicine, making such expenditures well justified. On the other hand, funds allocated to such projects must be diverted from research on other topics much more directly related to the core NIH and NHGRI mission: the improvement of human health. Funding studies of issues arising from nonmedical applications of genomics could also provide a disincentive for those agencies whose missions are much more closely aligned with the specific underlying subject matter (e.g., the US Departments of Labor, Education, Justice, and Defense) to allocate a portion of their own resources to the support of such research.

Related issues arise with respect to ELSI research with an explicitly international focus. Historically, ELSI Program support for international initiatives has frequently come more in the form of staff time than of research dollars. For instance, ELSI Program staff members have had extensive involvement in the coordination of international working groups to provide guidance on the bioethics components of the International HapMap Project (**http://hapmap.ncbi.nlm.nih.gov**) and 1000 Genomes Project (**http://www.1000genomes.org**). They also provide staff support for the bioethics components of some NIH Common Fund and other multi-institute programs [the

Cancer Genome Atlas (**http://cancergenome.nih.gov**), Human Heredity and Health in Africa, and the Human Microbiome Project]. However, the program in most years has allocated relatively little funding to projects designed to be carried out in other countries, except for countries in resource-poor parts of the world, where the program has had much more of a presence (99). This practice has been due in part to NIH administrative rules, which apply heightened criteria to the funding of grants for non-US investigators or with foreign components (108). However, it also reflects the program's reluctance to divert significant resources to the support of research in other developed countries that could, and arguably should, be supported by those countries' own funding agencies. Over the years, recognizing the importance of addressing ethical issues at the same time as the underlying science is conducted, funding agencies in Canada and the United Kingdom as well as organizations in a few other countries have begun to support some research on genomics-related or other bioethical issues. However, most of the existing programs have relatively modest budgets, and some define ELSI (or the analogous terms used locally) quite loosely, to refer more to public education and outreach activities than to scholarly research.

The Genomics and Society Working Group has now been charged with making recommendations regarding a process for periodic reassessment of the ELSI Program priorities in light of the current, increasingly constrained, NIH budget situation. However, as long as the ELSI Program continues to fund a disproportionate share of research in this area (relative to the research funded by other NIH institutes, other federal agencies, and funding agencies in other countries), the challenges raised by the need to make difficult priority trade-offs will almost certainly persist.

International HapMap Project: an international initiative to develop a publicly available resource describing the common patterns of human genetic variation

1000 Genomes Project: an international initiative to develop a deep catalog of genetic variation by sequencing thousands of diverse participants

The Cancer Genome Atlas: an initiative to catalog genetic mutations associated with specific cancer types using genome sequencing

IMPACT OF THE ELSI PROGRAM

Assessing the impact of the ELSI Program is challenging for several reasons. First, as is the case for many NHGRI extramural research programs, a portion of the studies funded by the ELSI Program involve basic research (e.g., the clarification of terminology and concepts or the analysis of moral frameworks, values, or cultural constructs). Basic research of this kind does not always have a direct impact on policy or practice, but it does help to provide a foundation on which more applied studies can be built.

Second, although all of the issues addressed by both basic and applied ELSI research are important, not all of them have direct relevance to specific policy enactments. This is the case, at least, if policy is defined narrowly as the passage of a statute, the release of a regulation, the establishment of a professional guideline or recommendation, the issuance of a judicial decision, or the formal adoption of some other official or quasi-official pronouncement.

Third, the trajectory between the dissemination of ELSI research findings and the establishment of research, clinical, or broader societal policies related to genomics tends to be nonlinear. Often, for example, the impact of ELSI research has come less from the direct translation of published study findings into a formal embodiment of policy than from ELSI investigators—operating independently as scholars, beyond the immediate scope of their NIH-funded activities—serving directly on particular commissions or other policy-making bodies or providing expert testimony or other forms of expert analysis to those groups. Some of these groups operate at the national level, whereas others operate at the international, state, or local institutional level.

Arguably the most consequential impact of ELSI research has come about in even more subtle ways, such as through the contributions the studies have made to incremental changes in the cultural milieu in which genomics research is conducted, genomic medicine is implemented, and genomic information is incorporated into decision making in various areas of society more broadly.

These gradual impacts, although difficult to measure, have become undeniably observable over a period of years.

The discussion below, although by no means exhaustive, provides a general overview of some specific ways in which ELSI research has been influential in each of these areas. Examples of impact can most readily be seen as falling into three categories: practices and policies related to genomics research, practices and policies related to genomic medicine, and broader social policies. These categories correspond to the four categories of current research priorities discussed above, but for the sake of efficiency, when considering the impact of the research, the third priority area—legal and policy issues—will be subsumed into the other three. This reflects the fact that, as noted above, the impact of research on legal and public policy issues can most often be seen in the direct enactment of laws or the implementation of public policies related to genomics research, genomic medicine, or broader societal issues.

Impact on the Conduct of Genomics Research

The impact of ELSI research has arguably been greatest in the area of policies related to the conduct of genomics research. This is probably a reflection of the fact that, at least until recently, when genomic medicine began to make its way into the clinic, basic research has been the primary area of underlying activity in the field of genomics.

One example of the impact of ELSI research in this domain can be seen in the evolution over the past 20 years of approaches to informed consent for genetics and genomics research and testing. Early explorations of the risks and benefits associated with genetics research (6, 15, 39, 48, 49, 111, 120) led to major changes in the way investigators draft, and the way institutional review boards review, consent forms for genomic studies. Although some of these changes have likely been responsible, at least in part, for the trend toward consent forms becoming overly long and complicated, more recent research on the comprehension of informed consent language by genomics research participants (11) is leading to the development of new models for simplifying consent documents and for streamlining the informed consent process.

Research on the need for a balance between the promotion of broad data sharing and the need to safeguard the privacy, autonomy, and related interests of genomics research participants (10, 54) influenced the development of the NIH policies for genome-wide association studies and genomic data sharing (93); more recent research on these issues is providing an evidence base for the evaluation of the effectiveness of these policies and for the identification of ways they can be improved (1, 8). Research on limitations in the ability to reliably deidentify genomic samples and the social and ethical implications of those limitations (59, 61) influenced the development by the Office of Human Research Protections of proposed revisions to the Common Rule (131).

Early work on the ethical issues relating to the use of stored genetic samples (25) influenced the initial development of policies and practices for biobanks and biorepositories at the NIH and other research institutions (66); more recent research is leading to the development of innovative governance mechanisms for these entities (8, 37). Recent research on legal issues associated with the application of the Clinical Laboratory Improvement Amendments in the context of genomic sequencing research has prompted preliminary discussions with the Center for Medicaid Services about possible reinterpretations of the law (32).

ELSI research has also had an impact on the way the interests of socially defined groups are treated in genomics research. For example, ELSI research on community engagement, community consultation, and group interests in genetic variation research (34) and on ethical and social considerations in the labeling of populations defined by ancestral geography (122) led to the development of novel protocols to engage and consult with the socially defined communities that

were approached to provide samples for the International HapMap Project and 1000 Genomes Project (121). It also led to the adoption of a more precise and ethically sensitive nomenclature for the populations studied in those projects and in subsequent genetic variation studies. More recent studies of novel approaches to community-based participatory research (50, 55) are serving as a model for genomics research conducted with Native American tribes and with other groups whose relationship to genetics and genomics research historically has often been contentious.

Impact on the Implementation of Genomic Medicine

The ELSI Program has had considerable impact on the evolution of policies related to the use of genomic information in the clinic. Many of the early funded studies of ethical and social issues in population-based screening (5, 24), carrier testing (20, 33), prenatal testing (13, 118), newborn screening (14, 139), and predictive testing of both children and adults for both early- and late-onset conditions (17, 19, 130) contributed directly to the development of a number of Points to Consider documents, recommendations, and guideline statements issued by professional organizations, and occasionally to enactments by other policy-making bodies (3, 26, 116, 119, 127, 128, 140).

More recently, as the more traditional technologies used in screening and testing have begun to give way to whole-exome and whole-genome sequencing approaches and as new recommendations have emerged on the handling of incidental findings in the arena of clinical care (42), ELSI research—including important normative work—continues to inform the ongoing policy dialogue (18, 38). Concurrently, studies of the attitudes of research participants and patients about the return of results (43, 53) and studies of the experiences of customers of direct-to-consumer genetic test marketing companies with receipt of genetic results (12, 52, 63, 138) are contributing to researchers' and clinicians' awareness of what people want and expect, how they perceive risk, and how complex genomic information can be communicated in ways that are easier for people to comprehend.

Broader Legal and Societal Impact

ELSI research has left its mark somewhat less frequently in the form of concrete legal or policy enactments with sweeping societal impact than in the more circumscribed realms of genomics research and genomic medicine, but in those cases in which its broader impact has been felt, the effects have been far reaching. For example, many of the early normative and legal analyses relating to genetic privacy and the risk of genetic discrimination (6, 36, 39, 48, 49, 111, 120) helped create significant momentum that led to several federal enactments. These include a provision in the Health Insurance Portability and Accountability Act of 1996 (Pub. L. 104-191, 110 Stat. 1936) prohibiting group health insurers from excluding individuals from group coverage based on genetic predisposition, Equal Employment Opportunity Commission guidance suggesting that discrimination based on genetic predisposition is prohibited by the Americans with Disabilities Act (134), an executive order protecting federal employees from genetic discrimination in the workplace (135 at 902-45), and, eventually, passage of the Genetic Information Nondiscrimination Act of 2008 (Pub. L. 110-233, 122 Stat. 881), which prohibits genetic discrimination in most areas of health insurance and employment.

In the area of forensics, research on ethical, legal, and social issues related to uses of DNA in the courtroom (112, 123) has helped to sensitize judges, lawyers, civil liberties advocates, and members of the law enforcement community to the issues involved in the collection and potential use of DNA samples from people brought into the criminal justice system. Research on the ethical and social implications of emerging behavioral genetics findings (113, 125) has, at least arguably,

led to greater media awareness of the need for nuanced discussions of this issue and has heightened awareness among judges and others involved in the legal system of the complexities associated with using behavioral genetics evidence in courtrooms and other societal settings.

Finally, studies and legal and economic analyses regarding the effects of gene patents and other types of intellectual property protection on genomics research and on access to genetic and genomic tests have provided crucial data that have helped to inform policy development in this area (47, 115, 117). For example, findings from studies supported by the ELSI Program were relied upon heavily in a report by the Secretary's Advisory Committee on Genomics, Health, and Society (124), which in turn became part of the evidence base made available to the US Supreme Court in the 2013 *Myriad Genetics* case (7).

INTEGRATING ELSI RESEARCH WITH GENOMICS RESEARCH AND POLICY ACTIVITIES

Many of the impacts of the ELSI Program just summarized can be attributed, at least in part, to increasingly close interactions between the ELSI and genomics research communities, and between ELSI research and policy activities. Although such interactions have always been a feature of the program, they have been occurring more frequently over the past 5–10 years.

On the research side, as noted above, the CEER Program (68) has as an explicit goal the building of transdisciplinary research teams that include both ELSI and genomics investigators. Several Common Fund projects and other large community resource projects coordinated by the NHGRI also provide a growing number of opportunities for interactions between genomics investigators and those with expertise in the ethical, legal, and social issues that those projects raise. Opportunities have come about through stand-alone RFAs issued to support ELSI research to be conducted in parallel with the corresponding genomics initiatives (Human Heredity and Health in Africa and the Human Microbiome Project); through the establishment of working groups for large initiatives (the Human Microbiome Project, the International HapMap Project, and the 1000 Genomes Project) to provide guidance on particular issues; and, occasionally, through the direct embedding of ELSI research within genomics research protocols (74, 76, 86, 98, 102).

On the policy side, as noted above, investigators supported by the ELSI Program over a number of years who are now well recognized as experts in the field frequently contribute to the development of policy at various levels. Many of these activities take the form of participation in various policy bodies, such as the Secretary's Advisory Committee on Genetics, Health, and Society (109); the Secretary's Advisory Committee on Human Research Protections (133); the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (132); and most of the major professional societies related to genetics. Investigators in the CEER Program, who have as an express mandate to facilitate the translation of ELSI research findings into policy, have been especially active in this regard, but many investigators outside of the CEERs also maintain an active policy presence. Within the NHGRI, the work of ELSI Program staff is also becoming increasingly integrated with the NHGRI's policy activities. In fact, one important reason for the formation of the new Division of Genomics and Society within the NHGRI was explicitly to encourage such further integration so that the research being funded can inform policy activities and so that policy needs can inform the research agenda.

Benefits of Enhanced Integration in the Research Arena

Increasing integration between the ELSI research enterprise and the genomics research and genomics policy enterprises carries with it a number of significant benefits. Initiatives encouraged

by the ELSI Program in which ELSI research is directly embedded into an active, ongoing genomics research project, such as the current Clinical Sequencing Exploratory Research Program, have afforded an excellent environment for conducting at least some types of ELSI research (e.g., empirical explorations of the experiences of research participants, patients, researchers, and clinicians) by providing a "natural laboratory" for conducting such studies. Studies of this type can often generate more reliable findings than those generated in more hypothetical studies, in which people are asked only in the abstract what they think about certain topics (e.g., about the relationship between genetics and racial or ethnic differences) or how they think they would react in certain situations (e.g., if they were to learn that they or their family members were at increased genetic risk for an untreatable condition).

Clinical Sequencing Exploratory Research Program: an initiative to explore practical and ethical challenges in the clinical use of genomic sequence data

Even collaborations that do not involve the direct embedding of ELSI research into genomics initiatives have proven beneficial in important ways. For example, some ELSI researchers find the opportunity to conduct research with direct policy relevance more rewarding than research that is purely theoretical. In addition, collaborations between ELSI investigators and genomics investigators have in many cases led to greater sophistication in the ELSI community about genomic science and greater sophistication in the genomics community about the empirical and normative methods used by ELSI investigators—which, in turn, has other benefits.

Over the years, for example, as ELSI investigators have learned more about genomics, the underlying science has increasingly informed the way they ask questions in their research. An examination of the papers emanating from some of the most recent studies (41, 58, 129, 137) suggests that this has led gradually to more well-informed studies with greater practical relevance to genomics practitioners. As a by-product of this development, there is evidence to suggest that genomics scientists on the whole have become less inclined to dismiss those who conduct ELSI research as fearmongers, privacy zealots, or irksome crusaders doggedly in pursuit of new ways to "squeeze the research pipeline." Researchers and clinicians appear increasingly to value the contributions of ELSI investigators to their work; in fact, many now actively seek them out for guidance on ways to design genomic and clinical studies or to integrate genomics into their clinical practices in an ethically (and legally) defensible way—even when doing so is not required by the funding opportunity announcement (23).

Correspondingly, in the ELSI research community, rumblings about the inherently "eugenic" or potentially "racist" nature of the genetics and genomics enterprise are today much less frequently heard. Far from signaling an abandonment of concern about potential misuses of the science, however, this change may simply signify greater nuance and sophistication in the way questions about contentious issues are now being addressed. Today's ELSI studies, for example, are more likely to involve focused examinations of issues such as the ethical and legal dimensions of genetic enhancement (9, 64), applications of behavioral genetics in specific contexts (113, 126), and approaches to research design, population labeling, and results reporting in studies of global genetic variation (35, 122).

Within the ELSI research community, concerns are sometimes expressed that this reorientation could lead to a premature diversion of attention from consideration of the broader issues underlying the many documented abuses of genetic knowledge that have historically occurred and that still occasionally take place (see also sidebar, Does the ELSI Program Perpetuate the Notion of Genetic Exceptionalism?). On the whole, however, more focused attention to specific, here-and-now issues raised by particular genomic technologies seems to be promoting more constructive dialogue and greater respect for ELSI research among genetics, genomics, and clinical investigators. This, in turn, is leading to studies likely to have a more measurable impact on the way the science is designed and conducted and the way the resulting findings are communicated and used.

DOES THE ELSI PROGRAM PERPETUATE THE NOTION OF GENETIC EXCEPTIONALISM?

Some discussions in the early ELSI literature, comparing genetic information to a "future diary," may unwittingly have overstated the deterministic and personal nature of genetic data compared with other types of biomedical information. Along with similar exaggerations from some proponents of genomic science, such characterizations may have contributed to the notion of genetic exceptionalism: the idea that the ethical concerns such information raises are unique. Today, the ELSI Program may be viewed less as a proponent of genetic exceptionalism than as a reflection of a commitment to a more socially responsible way of doing science, which agencies funding work in other biomedical and scientific disciplines have begun to emulate. For example, the National Nanotechnology Initiative has funded centers to study ethical issues in nanotechnology and encourages the incorporation of research components focused on such issues into their research and development programs (136). The Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative, announced in 2013, includes an explicit recognition of the need to explore the ethical implications of the science (114). In fact, both across the NIH and beyond, recognition is growing of the importance of studies that address bioethical issues arising in all areas of research—not just genetics and genomics.

Potential Drawbacks of Enhanced Integration in the Research Arena

Notwithstanding the many benefits associated with enhanced integration between the ELSI and genomics research enterprises over the past decade, it must also be acknowledged that increased integration has occasionally come with a price—especially for ELSI investigators who are funded through the CEER Program or under RFAs that require close collaboration or even the embedding of ELSI research within particular genomics projects. In fact, there is some early evidence to suggest that the growing demands for the inclusion of ELSI research components in genomic studies may be placing a strain on the relatively small pool of qualified ELSI investigators, who increasingly are being asked to participate in multiple such projects while continuing to pursue their own independent research agendas. As the time and energy of these investigators become increasingly diverted from their own work, there arises some risk that the depth and quality of ELSI research could eventually suffer. In addition, a risk exists that some ELSI investigators who face strong institutional pressures to serve as team players on integrated projects will be more cast into the role of "human subjects consultants" than regarded as truly independent experts, with deleterious consequences for the field.

It should also be noted that the enhanced mutual respect between ELSI investigators and genomics investigators resulting from closer integration discussed above has by no means been universal. Some persistent gaps in communication among investigators in the two fields are probably inevitable, given the differences in the cultures of the disciplines in which they have been trained.

Indeed, it is still not uncommon at some professional gatherings to hear genomics scientists—even those who have had considerable experience working closely with ELSI investigators—describe the methods of their ELSI research counterparts as "squishy." Correspondingly, pockets of resistance remain in some quarters of the ELSI research community to what they perceive as genomicists' sometimes overly technical orientation. Thus, for example, in discussions about genomic privacy, genomics investigators might tend to focus on the number of single-nucleotide polymorphisms required to match genotype data in one database to data in another, whereas ELSI investigators might focus instead on the governance mechanisms that need to be adopted and the cultural shifts that must occur to promote greater transparency and trust. The first

approach asks a question that can (at least potentially) be answered quantitatively, whereas the second asks a question that cannot. The latter question is more difficult to answer and produces solutions likely to be less clear cut and more complicated to implement; however, both questions are important.

Benefits and Potential Drawbacks of Enhanced Integration in the Policy Arena

Like closer integration between ELSI research and genomics research, closer integration between ELSI research and policy activities carries with it both benefits and risks. On the benefits side, such integration tends to increase the policy relevance of the research and maximizes the likelihood (though by no means guarantees) that policies related to genomics—whether in the sphere of research, clinical medicine, or society more broadly—will be solidly evidence based.

However, there are downsides as well. When ELSI investigators' time and energy are diverted from conducting research to focusing on policy translation, less overall research is likely to be conducted. In addition, some ELSI investigators report feeling mounting pressure to conduct translational research, or research with direct policy relevance, in contrast to basic or foundational research—even where the latter may, in fact, be the more critical long-term scientific need. Finally, some ELSI investigators have expressed trepidation about becoming essentially facilitators of others' policy agendas and concerns that the legitimacy of their standing as independent and autonomous academic investigators could be subtly undermined.

There are several other ways in which conceptualizing the role of ELSI investigators as being primarily policy fixers, and only secondarily producers of basic research in their own disciplinary fields, can be problematic. For example, ELSI investigators may be asked to produce solutions to vexing ethical problems that simply do not lend themselves to easy fixes (e.g., to come up with ways to recruit participants for genetic variation studies that are guaranteed to garner broad public acceptability, or to draft consent form language guaranteed to cover every conceivable future development). In addition, some ELSI investigators may experience subtle pressure to lean or slant the results of their research to support particular desired policy positions—or even avoid certain areas of inquiry completely—out of concern that their conclusions may be unwelcome by the funding agency from which they receive their support. Investigators in some cases may thus feel pressure to pull their punches when addressing sensitive topics, such as the ethical foundation of NIH data-sharing policies, or the cultural milieu that gives rise to hype in some media reports about the promise of genomics for the future of precision medicine.

THE FUTURE: REENVISIONING CHALLENGES AS OPPORTUNITIES

The challenges involved in promoting enhanced integration among ELSI research, genomics research, and policy development activities while simultaneously maintaining the objectivity, intellectual independence, and integrity of ELSI investigators have been well recognized since the inception of the ELSI Program (51, 60). To a large extent, these challenges arise from the simple fact that the program, although charged with supporting critical investigations into the ethical, legal, and social implications of genomics research, is organizationally, and indeed physically, situated within the very agency that supports the underlying science. Indeed, it is the very oddness of this coupling that, ever since the program's inception, has led to the suggestion—still occasionally voiced—that running a science ethics program out of a science funding agency is like asking the "fox [to guard] the chicken coop" (46, p. 438).

This is why, as mentioned at the outset of this review, the ELSI Program began as, and will always remain, an experiment. Yet it is also the reason that what might be viewed as a contradiction

can instead be seen as a unique opportunity for ELSI and genomics researchers to operate as partners rather than as adversaries. Continuing vigilance in addressing the inherent tensions raised by the program's very existence will be critical. It will also be critical to remain on the lookout for creative new ways to reenvision the inevitable tensions as opportunities to facilitate the conduct of genomic science in an ethically, legally, and socially responsible way.

SUMMARY POINTS

1. The Ethical, Legal, and Social Implications (ELSI) Program of the National Human Genome Research Institute (NHGRI) is currently the only dedicated extramural bioethics research program at the National Institutes of Health (NIH) and is by far the largest funder in the world of research focused on ethical, legal, and social issues in genetics and genomics.
2. ELSI research is highly multidisciplinary, with investigators from a range of disciplinary backgrounds and projects that utilize a wide range of both empirical and nonempirical research methodologies.
3. The ELSI Program faces significant priority-setting challenges because of the gradual shift within the field of genomics from an emphasis on basic research to an emphasis on research with identified human participants and immediate clinical applications, which carries with it an expanded array of ethical issues.
4. The ELSI Program increasingly faces challenges about whether it should continue to fund certain categories of research that could, and arguably should, be supported by other NIH institutes, other organizations, or funding agencies in other countries.
5. Research funded by the ELSI Program has had a significant impact on the way genomics research is conducted, the way genomic medicine is implemented, and law and society more broadly.
6. Although debates continue about whether research supported by the ELSI Program has had the effect of perpetuating the notion of genetic exceptionalism, the program may simply reflect the commitment by the NHGRI to a more socially responsible way of doing science, which some other scientific funders have begun to emulate.
7. Increased integration between ELSI research, genomics research, and policy activities has occurred in recent years, which may contribute to more informed and practically relevant ELSI research, the enhancement of mutual respect between ELSI investigators and genomics scientists, increased policy relevance and visibility of ELSI research, and the creation of more evidence-based policies related to genomics.
8. Increased integration of ELSI research with both genomics research and policy activities, although a positive development in many respects, carries with it some risk of compromising the autonomy, objectivity, and intellectual independence of ELSI investigators.

FUTURE ISSUES

1. The ELSI Program must continue to strive to strike an appropriate balance between investigator-initiated and program-initiated research.

2. The ELSI Program must continue to work closely with ELSI investigators to surmount certain unique challenges associated with the peer review of ELSI research grant applications.
3. With input from the Genomics and Society Working Group and the National Advisory Council for Human Genome Research, the ELSI Program must continue its periodic reassessment of research priorities in light of new and emerging issues as new technologies develop and as advances in genomic medicine occur.
4. With input from the Genomics and Society Working Group and the National Advisory Council for Human Genome Research, the ELSI Program must continue to assess the extent to which it can continue to fund certain categories of research that could, and arguably should, be supported by other NIH institutes, other organizations, or funding agencies in other countries.
5. The ELSI Program must continue to monitor the impact of its funded research and to strive for even greater impact.
6. The ELSI Program must continue to monitor the benefits and risks associated with enhanced integration between ELSI research, genomics research, and policy development activities, to make sure that the autonomy, objectivity, and intellectual independence of the investigators it funds are preserved.

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