The Genome Program's Conscience

A research program on the ethical, legal, and social implications of genome studies, launched as an "afterthought," is now the world's biggest bioethics program

In October 1988, James D. Watson, the Nobel Prize–winning geneticist, stood before a packed press conference to announce that he had been appointed to head biology's biggest and most ambitious single endeavor: the Human Genome Project at the National Institutes of Health (NIH). When asked about the social implications of this massive effort to decipher the human genetic blueprint, Watson announced—off the cuff, according to a former aide—that a fixed portion of the project's budget would be set aside for studies of how genetics research would impact society. Thus was created what Francis Collins, Watson's successor, calls "the largest investment in bioethics in the history of the world."

Over the past 6 years, Watson's spur-of-the-moment decision has steered $40 million of genome project funds into studies of the "ethical, legal, and social implications" (ELSI) of genetics research, creating in the process a unique amalgam of social, legal, and hard science studies—a model that is being copied in Europe and Japan. The ELSI program now gets a 5% slice of the budget of the National Center for Human Genome Research (NCHGR) at NIH, and 3% of the Office of Health and Environmental Research in the Department of Energy (DOE), NIH's partner in the Human Genome Project. Next year alone, the two agencies will spend $11 million on ELSI studies.

This huge investment should now be paying off, as the genome program spawns new findings and technologies that are challenging society's capacity to deal with them: Genetic tests for diseases such as cystic fibrosis, breast cancer, colon cancer, and sickle cell anemia are being developed or are already in use, at least in research clinics. Some people who test positive for disease genes are already finding it hard to get insurance, even jobs (see p. 621). And research into the genetic basis of behavior is provoking heated controversy. To learn whether the ELSI program is helping society cope with this genetics revolution, *Science* asked leading geneticists, ethicists, and genome program officials for their assessment of the effort so far.

"A mixed bag" is how Stanford University geneticist Paul Billings puts it, and that verdict is widely echoed. Billings adds that the program is making important contributions to ethics research, a point that the first chief of NCHGR's ELSI program, Eric Juengst—now director of the bioethics program at Case Western Reserve University in Cleveland—and other ESLI advocates underscore. They point to some practical accomplishments as well, such as a widely accepted set of principles to guard against genetic discrimination, echoed in a bill protecting workers against loss of insurance that passed Congress in August. But others say its biggest accomplishment has been to fill the library shelves with bioethics texts.

One reason for the varied assessments is the changing nature of the ELSI program itself. ELSI spent much of its money in the early days on conferences and analytical studies featuring many prominent bioethicists—efforts that swelled the bioethics journals with academic papers on genetics and society. In recent years, however, ELSI has been moving away from philosophy to concentrate more on technical problems, such as the genetic discrimination issue, ensuring quality in DNA testing labs, educating doctors in the use of genetic data, and guiding researchers on obtaining informed consent—"really critical issues that would not otherwise have found a home," says oncologist Kenneth Beutow of the Memorial Sloan-Kettering Cancer Center.

PAULINE LUBENS

Vexing Issues. Francis Collins supports ELSI but clashed with members of an advisory group.

But spending money on these issues doesn't necessarily mean ELSI or its grantees will reach a consensus on what should be done about them. Indeed, when the debate strikes close to home—as it did recently in a review of the ethics of using stored human tissues in research—the experts may agree to disagree. Another barrier to consensus is the incendiary nature of the issues with which it deals. Last year, for example, an ELSI-funded conference on genes and crime drew the wrath of activist groups (*Science*, 29 September 1995, p. 1808). And earlier this year, Collins clashed with members of the ELSI Working Group—a panel of outside advisers who help guide the program and have issued ethics policy statements—over the group's proposed research plans, which included exploring the volatile topic of genes and behavior. Collins vetoed their agenda, saying the agency couldn't afford it. Some members of the Working Group felt that their independence had been curbed. Two, including the chair, resigned.

Since then, Collins has commissioned an independent review, due in December, of the working group's structure and purpose presumably to help determine its fate. At the same time, the new chair of the ELSI Working Group, sociologist Troy Duster of the University of California, Berkeley, says that the Working Group should be moved out from under NCHGR's control. In a 15 August letter to the review panel, Duster argued that the Working Group, because its concerns are "much broader than the technical and laboratory aspects" of NCHGR, should report directly to a Cabinet-level office or to Congress. Duster also has said he would favor a general review extending beyond the Working Group to all of ELSI.

A blurry mandate

Assessing ELSI would be difficult, though, because it was created, Duster claims, as an "afterthought" to the genome program and for that reason has a blurry mandate. Its official task is not just to analyze ethical issues, but to "define … and develop initial policy options to address them." But ELSI does not have a public process for ranking issues that need attention.

In the early days, many looked askance at the entire ELSI undertaking, a curious science-ethics hybrid. When NIH leaders were briefed on ELSI, Juengst wrote in the Summer 1996 issue of *Social Philosophy and Policy*, "a senior NIH official" grumbled: "I still don't understand why you want to spend all this money subsidizing the vacuous pronunciamentos of self-styled 'ethicists.' " Collins acknowledges that "there has always been a two-culture problem between the ELSI types and the science types." Some of the science

ELSI's Cystic Fibrosis Experiment

In 1989, a group of biologists that included Francis Collins, then a professor at the University of Michigan, identified a genetic defect that causes cystic fibrosis (CF). Almost immediately, geneticists began to worry how it might impact society. Several journals, *Science* among them, warned of a tidal wave of genetic testing as companies rushed to market diagnostic kits. One paper envisioned a "billion-dollar industry" operating in a realm where there was "little formal guidance or regulation," with patients learning about their status as carriers of the primary mutation, delta F508, from doctors too ill-informed or hurried to provide good counseling.

The tidal wave never struck, and a set of studies funded by the program in Ethical, Legal, and Social Implications (ELSI) at the National Center for Human Genome Research (NCHGR) suggests it's not about to. The consortium—ELSI's first clinical look at the difficult social issues that come with a new genetic test—hasn't yet published its conclusions. But the early signs are that worries about counseling and informed consent were justified. The investigators also found something quite unexpected: People who are offered a test that doesn't have a bearing on their own health don't go for it unless they are about to have a child who may be affected.

Widespread use of the test was prevented, in part, because the American Society of Human Genetics came out against screening for CF in 1990 and 1992, on the grounds that the test wasn't sensitive enough. Meanwhile, after other agencies that fund basic research on CF declined to get involved in these clinical-social studies, NCHGR issued grants to seven investigators—an unusual group of psychologists, ethicists, and geneticists. Their goal: to scout the territory and report back on what might happen if testing for CF genes were expanded throughout the nation.

The CF consortium was to be a new type of biomedical research. It aimed to assess the social impact of genetic technology by trying it on a small scale and extracting general policy recommendations. This model was used again in 1994, when ELSI funded a second, even bigger consortium; this one focused on genes that increase a person's own risk for breast or colon cancer (see p. 496).

In an effort that ended a year ago, the researchers gathered data on how 20,000 people reacted when offered a test to determine if they carry a mutation in the CF gene. (Carriers show no symptoms of the disease but risk having offspring with CF.) Although the policy recommendations are still in the offing, most of the CF investigators have published independent reports or have papers in press.

Their main finding, "which surprised everybody," according to Collins—now NCHGR's director—is that the public responded "coolly" to the offer of CF testing, except for couples already involved in a pregnancy. And even parents-to-be seemed to want the test only if it was part of a broad prenatal screen, Collins says, such as one that also checks for neural tube defects and Down syndrome. Outside that context, "people just don't seem to be all that interested," Collins says, "especially if it's going to cause them some inconvenience or cost them some money." People just aren't that eager to find out about their genes.

The team at Vanderbilt University in Nashville, Tennessee, for example, found that less than 1% of the people who received the offer of a free test sought it. The Johns Hopkins University group found that only 3.7% of those offered a free test came in if it required a special visit, and 23.5% turned up when the test was conveniently available immediately at a clinic. The team at North Carolina, led by medical sociologist James Sorenson, reported a better response when offering the test to relatives of CF patients. According to Sorenson, 58% of members of CF families interviewed took the test. The highest response was registered by a team led by Wayne Grody at the University of California, Los Angeles (UCLA). About 53% of the women undergoing prenatal screening at a health maintenance organization clinic took the test when it was offered free, and 77% in a similar clinic at UCLA accepted it.

But even among those who embraced the test, many found it difficult to understand the results. Peter Rowley's team at the University of Rochester was "distressed," for example, that just 44% of the women who tested negative understood that they might still give birth to a child with CF. (The test only detected about 90% of CF-causing mutations; current versions do better.) Equally "worrisome," the Rowley group reports, was the unenthusiastic response of physicians. Rowley's group says that when it contacted primary-care doctors and offered free CF testing on condition that adequate counseling be given to patients, 49% of doctors declined, largely because they didn't like the time-consuming consultative process. Those who did sign up spent little time explaining the test to patients. Rowley's group concluded, however, that patients could get information by reading a good brochure.

Although the ELSI consortium has yet to issue general conclusions, a draft report prepared for the consortium warns about the "malleability ... of demand," suggesting that patients might be pressured into accepting a test they may not understand or benefit from. The Vanderbilt team has concluded that, because the test is unpopular and creates some risk that those who test positive may lose insurance, "we believe that clinicians should not routinely offer carrier screening to nonpregnant individuals who do not have a family history of CF." Grody's group at UCLA, on the other hand, felt that their testing program provided valuable information to a large, ethnically diverse group. They concluded that CF carrier testing should be offered to certain high-risk groups.

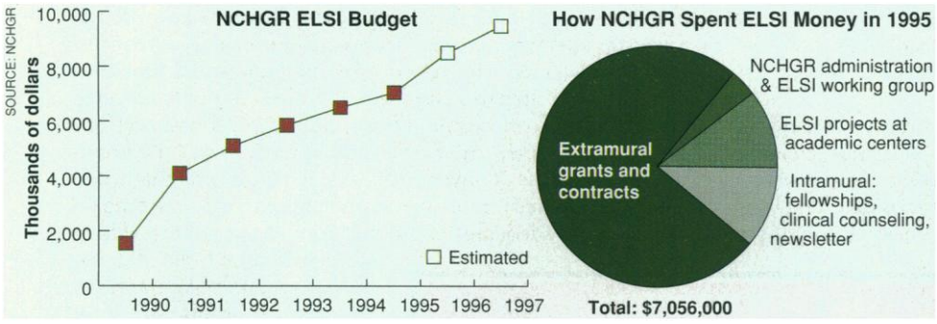
ELSI's task now is to forge this welter of data and mixed interpretations into policy recommendations, which it hopes to do at an NCHGR-sponsored meeting set for next April. The process is a "little delayed," as Neil Holtzman of Johns Hopkins University concedes, and it won't be easy. And the fact that it has been hard to reach closure on CF testing—a topic that has moved to the back burner—suggests that ELSI will have its work cut out as it tries to tackle the much more volatile topics of testing for cancer genes and, ultimately, genes that affect behavior. **–E.M.**

THE CF CONSORTIUM

Investigator	Location	CF test acceptance	Family/pop. study
Asch, D.	Univ. of Penn.	—	pop
Fanos, J.	Calif. Pac. Med. Ctr.	—	fam
Grody, W.	UCLA	53% to 77%	pop
Holtzman, N.	Johns Hopkins	4% to 24%	pop
Phillips, J.	Vanderbilt	<1%	pop
Rowley, P.	U. of Rochester	57%	pop
Sorenson, J.	U. of North Carolina	58%	fam

types looked on ELSI as a "welfare program" for ethicists, who "only talked, but didn't change the world," says Collins. ELSI policy wonks meanwhile thought that scientists and clinicians tended to ignore the consequences of their work.

This distrust was not helped by ELSI's early agenda, which concentrated heavily on conferences. One ethicist recalls that these early ELSI meetings were a traveling show in which familiar experts mulled over familiar issues at changing venues. And Watson himself concedes that he saw ELSI initially as a shield and a sounding board. "It kept us from being attacked" by those who were concerned about the consequences of genetic research, Watson says. But he recognized that the existence of genetic data banks would pose "genuine problems" to the individual and hoped ELSI would lead to new guarantees of privacy. Watson says he thought it was important to educate the public about their own genetic risks "so that they can make choices." The "great ethical failure," Watson says, "is having knowledge and not using it." The aim in funding conferences was "to get discussions started before we rushed" into genetic testing.



Steady growth. NIH's ELSI program gets a 5% share of genome project funds; it spends more than two-thirds of its budget on extramural grants and contracts.

ELSI's supporters also point out that the program has always funded a broad array of activities beyond these public gatherings. Today, NCHGR's ELSI spends more than two-thirds of its budget on extramural grants and contracts. From its inception in 1990 through 1995, according to a summary prepared by Elizabeth Thomson, deputy director of NCHGR's ELSI, it has funded more than 125 projects, resulting in the publication of more than 150 articles and books. They cover a wide range, including a public television series on genetics, a book by Leroy Hood and Daniel Kevles (*The Code of Codes*), educational materials, a study of patents and genetics, research on how to educate clinicians, and scores of studies of genetic testing. DOE, meanwhile, has used its ELSI money to develop a high school genetics curriculum, fund a model genetic privacy law, and hold seminars on genetics for judges.

A more practical bent

The ELSI program shifted its focus in 1992, when it began digging into the gritty details of clinical genetics. In that year, it launched the most ambitious study ever attempted of the introduction of a new genetic test: a screen for the genetic defect that causes cystic fibrosis (CF). The study, conducted by seven investigators around the United States, focused on the social and psychological impacts of testing, and it came up with a surprising conclusion: Although the test was initially expected to be in great demand, few people, in fact, had much interest in taking it (see p. 489).

Although the CF consortium has not published general conclusions, Thomson says it has helped to develop better consent forms and educate ELSI managers on how to coordinate research. Indeed, NCHGR is using the CF study as a model for a study examining the risks and benefits of tests to detect breast and colon cancer susceptibility genes. A consortium of 11 investigators is now turning in data on these tests (see p. 496).

ELSI chiefs also point to several important accomplishments in the policy arena. An extramural group led by Thomas Murray of Case Western Reserve made recommendations on how to prevent discrimination in insurance that are echoed in other ELSI statements and are now part of mainstream thinking in Congress. In a related move, ELSI staff nudged the Equal Employment Opportunities Commission into ruling that a person who tests positive for a disease gene may be viewed under the law as having a disability and therefore be protected against discrimination by employers. And a 2-year-old task force chaired by Neil Holtzman of Johns Hopkins University is drafting what Collins describes as "muscular guidelines" for controlling the quality of genetic tests, to be issued next spring.

ELSI's attempt to forge a single policy on something that directly affects researchers—ethical standards for the storage and use of human tissues—has been less successful. A task force of experts led by an extramural ELSI researcher, Ellen Wright Clayton of Vanderbilt University in Nashville, Tennessee, negotiated draft guidelines for more than a year starting in mid-1994, then published recommendations last December in the *Journal of the American Medical Association*. The report notes that experts could not agree on all issues. For example, they differed on whether it is acceptable to store tissue samples without consent if samples are stripped of personal identifiers. Some said it was; others said it was not—that consent must always be obtained if possible. And the report recommended that patients be given a complex set of options on the use of tissues in research, along with warnings about the "potential consequences." Since then, several organizations, including the College of American Pathologists, have issued independent views.

Collins is now turning to the president's newly impaneled National Bioethics Advisory Commission (NBAC) to ask for a ruling on this issue. It's not clear whether NBAC will take up his request. Nor is it clear how NBAC and ELSI will handle shared concerns in the future.

Collins's move to seek outside advice is part of a more aggressive effort to translate ethical debate into public policy—a move that some observers say has long been needed. Policy analyst Kathi Hanna, for example, wrote in a 1993 paper published by the Institute of Medicine that the ELSI program lacks a "clear-cut mechanism" for focusing on practical issues and transmitting findings to policy-makers. Many ethicists, including philosopher Daniel Wikler of the University of Wisconsin, Madison, agree. But some researchers, including Juengst and Billings, caution against focusing ELSI studies too heavily on specific goals at the expense of independent inquiry. ELSI could become "politicized," Billings warns.

Collins, for his part, is satisfied that ELSI supports a "cadre of really superb, world-class investigators who come at these problems from various directions" ranging from theology to law to basic science. And at the same time, Collins says, ELSI has made "substantial progress" in getting "all of that scholarship turned into policies that actually protect the public."

Keeping those competing interests in balance will be a challenge that is likely to become increasingly difficult as the genome program becomes more deeply involved in the world of applied medicine. Nobody with whom *Science* spoke doubted the wisdom of Jim Watson's decision to involve the genome program directly in ethical, legal, and social studies of its own products—or the scale of the challenges this effort will face in the years ahead.

–Eliot Marshall