Who Owns the Human Genome?

Questions are mounting about whether anyone can "own" the human genome—whether it can be copyrighted or patented—and what effect that might have on a federal collaboration

This is the first of two articles exploring current developments in the initiative to map and sequence the human genome. The second will focus on organization and funding.

HARVARD biologist Walter Gilbert did not attend a recent workshop on mapping and sequencing the human genome, but he was clearly on everyone's mind. As the Department of Energy (DOE) and the National Institutes of Health (NIH) continue jockeying over which agency should lead the federal effort and how it should be structured, a new set of questions has emerged. What will be the effect of this proposed project—the biggest yet undertaken in biology—on open scientific communication? Will researchers hold close their results because the stakes—both financial and professional—are so high, thereby slowing the search for medically important genes?

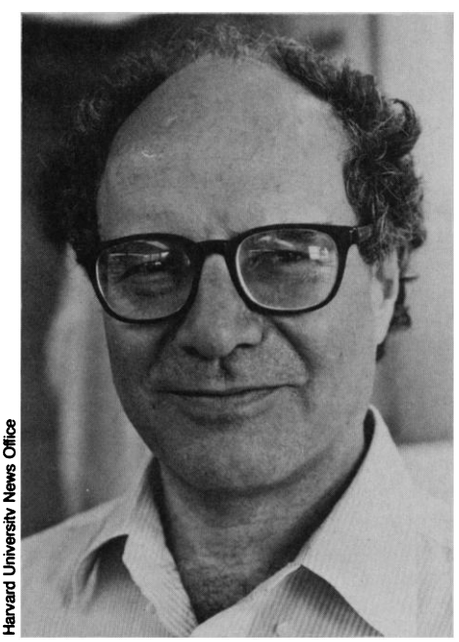
Can anyone "own" the human genome? If a company sequences a gene or chromosome, does it have proprietary control? And specifically, can Gilbert really copyright the human DNA sequence, as he says he plans to do with his new company, Genome Corporation.

"There is scientific apprehension that materials won't be available, that researchers will have to repeat work, and that the government will have to keep funding duplicative work," said Robert Cook-Deegan, an analyst at the Office of Technology Assessment (OTA) who organized the workshop as part of the project he is directing on the human genome initiative.*

Some say the effects of the proposed project are already being felt throughout the genetics community. "Until now U.S. researchers have been generous in exchanging clones," said C. Thomas Caskey of Baylor College. "Every molecular biologist in the United States knows the term 'cloning by phone.' But now I'm definitely detecting a tightening of this attitude as I call my friends."

The workshop, which was cosponsored by OTA and the Howard Hughes Medical Institute, focused on barriers to collaboration in a large federal project. The Hughes Institute, a nonprofit organization, is now spending about $1.5 million on research related to mapping and sequencing. In the free-ranging discussion, which included key researchers, ethicists, lawyers, and representatives from industry and public and nonprofit agencies, there were clearly more questions than answers. But the general consensus seemed to be that problems will worsen unless mechanisms are set up in advance to ensure the open exchange of information and materials.

The questions raised at the workshop are not particularly new, now that the majority of the nation's leading molecular biologists have corporate ties of some kind. Yet they seem particularly worrisome in regard to efforts to map and sequence the human genome. As Leroy Hood, a Caltech biologist who is one of the leaders in developing automated technologies for mapping and sequencing, told *Science*, "Some people are willing to share information and some are not. That hasn't changed over the past 10 years. What could affect it is if you can copyright or patent sequence data."



Harvard University News Office

Walter Gilbert: *Genome Corporation "will create a catalog of all human genes [which] would be made available to everyone—for a price."*

Unlike the rest of biotechnology, in which patenting engineered microbes and animals is becoming commonplace, there seems to be something inherently different—and emotionally charged—about anyone laying claim to the human genome, or even a chunk of it. "Being able to copyright the sequence would make me very uncomfortable," said Frank Ruddle of Yale. And Caskey asked if there is a precedent for saying, "This information is so important that it cannot be proprietary. This is the first time we'll ever get this information on man—can we make a special case?"

In addition to these issues surrounding ownership of the genome, other things set this project apart from the rest of biology and fuel concerns about scientific exchange.

One is the vast clinical applications and huge profits expected to emerge from such a project, which may exacerbate tendencies to withhold results. Mapping the genome will enable investigators to pinpoint the exact location of genes associated with the 3500 or so known inherited disorders and may also provide insight into numerous diseases, including cancer, diabetes, and heart disease, in which genetic predisposition plays a role. Working out the exact nucleotide sequence of these genes and the regions that control their expression may reveal techniques for early diagnosis or perhaps treatment.

"Working out the sequence and mapping genes to certain areas has a real monetary value," said Ruddle. "It can be sold. That's all to the good, it gives people an incentive to pursue it. But at the same time, not all will be given access, some may be locked out."

With a project of such immense potential, George Cahill of the Hughes Institute summed up succinctly, "we have to look at the bucks to ethics ratio."

This undertaking also differs in intent from most biological projects. "The goal of this project is to create a national resource of information on the human genome—avail-

* The workshop, "Issues of Collaboration for Human Genome Projects," was held 26 June in Washington, D.C.

able to all," as Cook-Deegan describes. "That implies a type of data sharing that might be different from normal science. If we have a concerted effort, then we need people to talk to each other."

As yet there is no centralized, interagency human genome project—DOE and NIH are pursuing their own initiatives—but there is general agreement on how to proceed. The first stage would be to develop a physical map of the genome—a set of overlapping DNA fragments that span the entire genome—and then to locate genes and markers on it. (The latter process is often referred to as developing a genetic map.) This would be accompanied by a simultaneous effort to develop technologies for rapid mapping, cloning, and sequencing. The second stage, which might follow in 5 years, would be to work out the nucleotide sequence of regions of interest, if not the entire genome. As sequence data and materials accumulate, they would be put into a repository where they would be available to other researchers.

Charles DeLisi of DOE, who instigated the entire effort a couple of years ago, uses the analogy of an accelerator. The goal, he says, is not to answer fundamental questions but to develop a tool to make that work possible. And if this massive and expensive project is to be completed in a reasonable time, new information and methods must be rapidly disseminated among the numerous collaborators.

"In the normal scientific mode the researcher is under no obligation to send out materials or information before he has published," Cook-Deegan says. "But in this case, the agencies might want something different, for investigators to be more open."

DOE and NIH have begun talking about how to set up a database and repository, but numerous nitty-gritty questions concerning access, intellectual property protection, and how to ensure that collaborators enter their data promptly remain to be addressed, he says.

These questions will be central not just to the human genome project but to the rest of biology as well, said David T. Kingsbury of the National Science Foundation. "More large centers of data generation are beginning to emerge, and they will generate more data than they can interpret. In response, the role of scientists will change: they will become more interpreters of data. If those centers we are starting don't put their data on-line immediately, we are in trouble."

Throughout the OTA meeting the conversation kept coming back to Gilbert and his plans to copyright sequence data. There was palpable unease, as well as considerable uncertainty, about what he actually intends to do. Much of the discussion centered on whether he legally can claim copyright protection for the sequence. Opinion varied, even among the lawyers. Does deciphering and then writing down the sequence meet the test of originality necessary for a copyright?

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Thomas Osterling: *Collaborative Research, of which Osterling is president, has filed a patent application for "the probe and any other probe between that one and the gene."*

"One view, which is not widely shared, is that you can copyright sequences," said Susan Rosenfeld of the science and law committee of the Association of the Bar of the City of New York. "This view holds that DNA is like a computer program, so it can be copyrighted." Rosenfeld challenges this view, however, and says that most other attorneys do as well.

Gilbert told *Science* that he can copyright the sequence because "someone worked it out and wrote it down—so the order of the letters is copyrightable, like a string of letters in a book." A number of other participants ceded him the point. As Rachel Levinson of the NIH director's office noted after the meeting, "If people didn't take Gilbert seriously, they wouldn't be worrying about it."

Cahill, for one, believes that Gilbert can copyright the format in which the sequence appears, if not the anatomy—the sequence itself. It's not the copyright per se that disturbs him, he told *Science*, but what it means for rapid exchange of information. "If Gilbert's data would be of value only before the sequence is out as public information, I don't see how he can make any money unless he sits on it, in which case he will engender hostility. It goes against all tradition in scientific philantrophy."

Gilbert does not see what all the fuss is about. "The idea of the company is to be a service to the biotech and pharmaceutical industries and to the research community . . . to answer questions that biologists have in doing research," he told *Science*.

His company, Genome Corporation, "will create a catalog of all human genes," probably starting with DNA from a placenta. The map and sequence data would be put into a database, along with other useful analysis, "where it would be made available to everyone—for a price." He declined to speculate on what the fee might be.

As he envisions it, researchers will log onto the database and ask any question, such as, where does this piece of DNA belong? As Gilbert explains, "the company will say, for a price, that the gene is on chromosome 21, 1,300,000 bases from the left. . . . A user can call up any part of it and read it. Or a pharmaceutical company might like a copy of the whole sequence; we could license it." He emphasizes that people would be free to use this information however they choose—except, of course, to reproduce it and sell it. "You can buy a book but you can't sell it. It is exactly that distinction."

What he is selling, Gilbert says, is ease of access. "Ease of access creates value. It does not have to be free to be of great use. It is like making restriction enzymes. Everyone is free to make their own, but they choose to buy them because it is cheaper. Here, it will be cheaper to ask the question than to work out the entire sequence yourself. "

He concedes that once someone else sequences the genome, the value of his database might decline. "That's a business risk. A competitor could move into the field. But where is the weight of information? Whoever starts first will end up by owning, by having in his possession, the whole database. Once someone has done it, it is in no one else's interest to do it again. It would be cheaper to pay for it."

All this depends, of course, on Gilbert getting there first. He is still shy of the $10 million in venture capital he says he needs, but he expects to be in business by midsummer. And, with a "reasonably sized company, about 200 people," he expects to complete the sequence in about 10 years, after spending the first couple of years on mapping and developing new technologies in several areas of activity, including sequencing.

He openly admits to being a "technologic optimist." Most other researchers believe that sequencing cannot be done quickly or economically until various cloning and sequencing technologies are automated, which is often estimated as at least a 5-year effort. To Gilbert, however, "it's not a question of new technology development, it's

technology application."

If Gilbert's plans were seen as the only challenge to open exchange of information, the issue might not be the subject of such intense debate. But other questions are arising because work that is key to mapping and sequencing the genome is also fundamental to developing commercial products. As a result, academic researchers are competing directly with corporate scientists, who by necessity operate under different rules of disclosure. This situation may be common to scientists in other fields. However, to many geneticists, who are now finding that they are denied access to scientific data, the situation is new and often extremely frustrating.

A relatively new type of marker—restriction fragment length polymorphisms (RFLPs)—is a case in point. RFLPs (pronounced rif-lips), which detect natural genetic heterogeneity among people, are an invaluable tool in searching for disease-causing genes, and they are indispensable in mapping the genome. RFLPs can also be fashioned into prenatal screening tests (linkage tests) to detect genetic disorders, which explains the commercial interest.

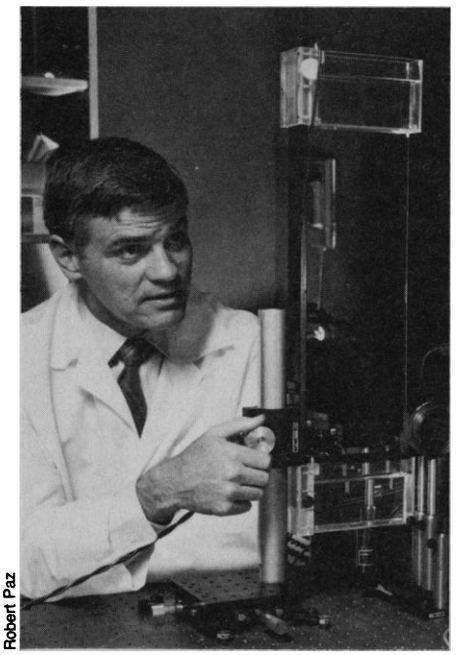
These markers indicate the approximate chromosome location—a region of perhaps 5 million to 15 million base pairs—of an unknown gene. From there, finding the gene itself is no small task, but it is far easier than searching for it throughout the entire 3 billion base pairs of the human genome.

Indeed, these markers made possible the recent localization of genes associated with Huntington's disease, cystic fibrosis, Alzheimer's disease, Duchenne muscular dystrophy, manic-depressive illness, and chronic granulomatosis disease.

As might be expected, competition is stiff to develop these markers. Much of this work is being done by Collaborative Research Inc. of Bedford, Massachusetts, and by Raymond L. White and his colleagues at the Hughes Institute at the University of Utah, although a few other companies are also gearing up.

Collaborative, whose declared goal is to be the leader in the field diagnostic tests for genetic disease and cancer, has spent $10 million to date on this work and has developed 500 to 600 markers, according to Thomas O. Oesterling, the president. David Baltimore of MIT is the chairman of Collaborative's science advisory board and is on the board of directors.

White's group also has some 600 markers: about 400 RFLPs and just shy of 200 variable number tandem repeat (VNTR) probes, a newer and, he believes, more informative type of probe. Both markers detect genetic heterogeneity: RFLPs by finding a single point mutation—a substitution in one base pair; VNTRs by finding repeated DNA sequences.



Robert Paz

Leroy Hood: *"Some people are willing to share information and some are not . . . What could affect it is if you can copyright or patent sequence data."*

White's probes, along with those of other Hughes Institute researchers, are deposited in the American Type Culture Collection, where they are available to other researchers; Collaborative's are not. Collaborative does lend its probes to some 40 to 50 academic collaborators, says Oesterling, under confidentiality agreements.

Linking a gene to a chromosome is a valuable first step, but it is not sufficient for developing a patentable commercial product. The problem is that the marker may be relatively far from the gene and thus may become separated from it during recombination. To develop an accurate screening test, closer markers are needed, preferably flanking ones.

That's where tension arises. If an investigator announces that he has linked a gene to a specific chromosomal region, others can pull out their markers for that chromosome and use them to find more informative markers. The competitive advantage to keeping quiet is undeniable.

In the grand scheme of things, a delay of 6 months or so would have little effect on the pace of scientific advance. But many find it disturbing nonetheless because it butts up against deeply held scientific norms. "What if someone finds the locus of a disease gene," Cahill asked at the workshop, "and then holds onto it so others can't do the work. How long can something be kept secret if it is for the general good? I don't know who is sitting on what now." Caskey pointed to the recent cluster of papers announcing the locus of the Alzheimer's gene. "It is unlikely that everyone discovered it at the same time."

Geoffrey Karny, a lawyer with the Washington, D.C., law firm Dickstein, Shapiro, and Morin, challenged the notion that industry will sit on something solely for proprietary reasons. "Researchers sit on stuff all the time until they are sure."

Similarly, George Gould, a patent attorney with Hoffmann–La Roche, does not anticipate problems with withholding. "The history of the past 6 years is that biotech companies have made information available to the public very quickly—far more quickly than patent attorneys would like." Gould says that he and most patent attorneys would like their scientists to delay publication for 18 months so as to improve the chances of getting a patent overseas. But typically, he says, "people will publish early to get scientific priority as well as patent priority."

"A key question for industry," said Bernadette Alford, a lawyer with Collaborative, "is how to protect our investment and collaborate with scientists. We need new mechanisms to protect our rights or it will not work." She says there are few obstacles to sharing clearly patentable products. "But other pieces of information, like the 300 to 400 probes we have developed, are hard to share. We won't file patents on 300 to 400 probes. For 90% of the work we do, we don't see how we can share it."

Collaborative was the first group to link the cystic fibrosis gene to chromosome 7. At the meeting Alford held out their handling of this discovery as ideal. "We found it on Monday and announced it on Wednesday." They have subsequently developed a panel of 12 markers, flanking the gene, that are being used in diagnostic tests, available in their laboratory for $1100.

However, a number of researchers told *Science* that Collaborative held back their results for several months until they could find more informative markers.

Alford denies the charge. "We had been working on cystic fibrosis for months. But once we could get positive scientific confirmation, we immediately announced it." Immediate announcement was possible, according to Alford and Oesterling, because they could envision a diagnostic test and thus filed for a patent. As Oesterling later explained, they filed a patent application for "the probe and any other probe between that one and the gene."

Their broad-ranging patent application, like Gilbert's copyright claims, does little to

relieve the simmering tensions.

"Their patent application seems unreasonable to me," says White, who points out that Collaborative essentially patented his work before he even did it. Since Collaborative's discovery, he and others have found closer, more informative markers. And the whole question may be moot anyway, White says. Robert Williamson of St. Mary's Hospital Medical School in London recently reported the identification of a candidate cystic fibrosis gene. If Williamson is right, says White, "it will completely blow Collaborative's test out of the water. It will become a useless panel of probes."

There is no knowing how the patent office will view Collaborative's application. The situation regarding patents for these products and processes, as for the rest of biotechnology, is hazy at best. Indeed, a patent application of the process for making RFLPs has been pending for 7 years. The application, filed by Stanford University, has been licensed to Collaborative.

Alford, however, is fairly confident of their claim. "We found the linkage to chromosome 7, and others began to look there," she told *Science*. "But one would argue that it is our teaching that led them there. We'll wait to see what the patent office says. But we believe that by identifying the locus with the RFLP, we are telling the world where to look for the cystic fibrosis gene."

Although these new arrangements pose challenges to scientific collaboration, several workshop participants were sympathetic to the predicament of Collaborative Research and other companies. "It's a Catch-22," says Cook-Deegan. "If a company behaves in what scientists believe is a socially responsible manner, they can't make a profit."

"Collaborative Research envisions themselves as world leaders in markers in the human genome," Kingsbury told *Science*. "They are worried about sending out probes that could be commercialized by their competitors. Frankly, I'm somewhat concerned about this. But I understand their concerns; probes are easy to duplicate. I'm not sure what kind of safeguards we need."

Clearly, new mechanisms will be needed as DOE, and perhaps NIH, step up their mapping efforts. DOE is already supporting mapping work on chromosomes 16, 19, and 21 at Lawrence Livermore National Laboratory in California, Los Alamos National Laboratory in New Mexico, and at Columbia University. And for fiscal year 1988, DOE has requested $12 million for the genome project, up from about $5 million for the previous year. David Smith, who runs DOE's human genome project, declines to comment on the budget request for fiscal year 1989. But a recent report by an advisory committee to the Office of Health and Environmental Research recommended that DOE's genome project receive $40 million for 1989, with steady increases up to $200 million a year by 1993.

Within a few months DOE will be issuing requests for proposals for mapping and technology development. And DOE would like to use Collaborative's markers in developing their map, Smith told *Science*. "There is a tension between maintaining the rights of people to realize that monetary value and between the goal of getting information into the public sector where it can do some good. We are talking with Collaborative. We are optimistic that we can maintain their proprietary interests and have markers available for mapping. It is not an insurmountable problem."

"We have a lot of probes, and we would like to participate," says Alford. However, without safeguards of some kind, Collaborative will not place its probes in a repository where they can be used by investigators working on the physical map, she says. In her view the best initial approach would be a repository that contained a complete list of information on the known probes, what they do, and who has them—but not the probes themselves.

One mechanism discussed at the workshop is a requirement, imposed on all researchers participating in the federal project, to make materials and information available at the time of publication or perhaps with a 1-year grace period. A possible model is the Centre d'Etude du Polymorphisme Humain (CEPH), the French database. CEPH sends out its materials with the stipulation that users in turn send their data back to CEPH. It also offers a degree of proprietary protection; a researcher may request that his materials not be made public for 1 year, though they are available to other CEPH collaborators.

Other large federal collaborations may also present useful models for meeting the dual objectives of ensuring information exchange while guaranteeing some form of proprietary protection. Two mentioned at the meeting were the federal programs to develop a malaria vaccine and AIDS drugs.

The key, the agency officials, lawyers, and scientists at the workshop agreed, is for agencies to set up in advance the requirements for information exchange and then condition grants on them. "Unless arrangements are created in advance," Cook-Deegan says, "some people will not collaborate."

■ LESLIE ROBERTS

A Younger Universe Is Seen in the Stars

A tricky observation of radioactive thorium in nearby stars leads to a surprisingly young age for the galaxy and for the universe; many astronomers are skeptical—but some are enthusiastic

At a time when most astronomers would agree that the oldest stars in our galaxy have been shining for some 15 billion years, anyone claiming that the universe itself is only 11 or 12 billion years old is bound to raise a few eyebrows. Yet Harvey R. Butcher, director of the Kapteyn Astronomical Institute in Groningen, the Netherlands, is claiming just that—and some researchers think he is right.

Butcher bases his conclusion on recent spectroscopic observations of the radioactive nuclide thorium-232, which he has measured in the sun and in 20 nearby stars that are like the sun. The 14-billion-year half-life of this isotope has long made it a favorite of researchers trying to do radioactive dating on cosmic time scales. Indeed, the standard figure for the age of our own solar system, 4.6 billion years, is in part derived from the relative abundance of thorium-232 and various uranium isotopes in meteorites and in moon rocks.

In Butcher's case, however, he compared thorium-232 with a different nuclide, neodymium-142, which happens to have a spectral line that originates in the same part of a star's atmosphere as the thorium line. This location makes it a particularly useful calibration standard, since there are no correc-