Biotech Firms Compete in Genetic Diagnosis

New probes also promise detection of infections and food contaminants, but field is still marked by uncertainty

Boston

BIOTECHNOLOGY firms are positioning themselves to cash in on an important new market they predict will emerge from rapid advances in the diagnosis of human genetic disease. Already, new methods for detecting genes that cause inherited diseases have led to tests for some of the most devastating genetic disorders. The tests are based on DNA probes that reveal genetic markers near the genes.

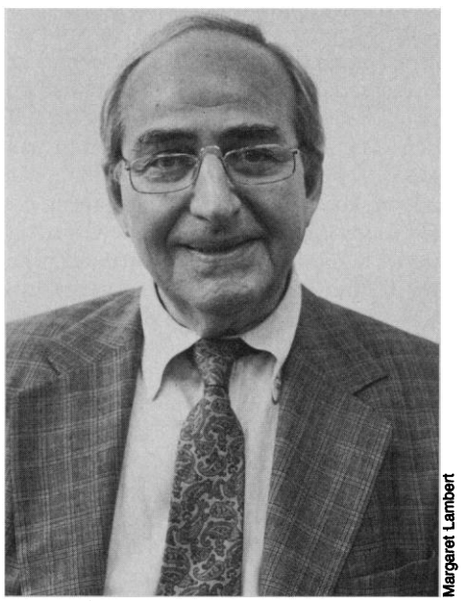
The current year has been especially fruitful. The first commercial tests for prenatal diagnosis of cystic fibrosis, the most common lethal inherited disease of Caucasians, became available in 1986; predictive testing began for individuals who might carry the gene for Huntington's disease; a portion of the long-sought gene for Duchenne muscular dystrophy was isolated; and a so-called "recessive oncogene" responsible for familial predisposition to retinoblastoma was discovered.

Genetic disease is only one area where DNA probes have opened new doors, however, and it is by no means the largest. Investment and development activity are in fact concentrated on the use of probes to detect food contaminants and infectious organisms. For example, because they can detect and identify microorganisms down to individual serotypes in a matter of hours, DNA probe–based tests could replace current assays that take days to complete. Faster identification of infectious disease organisms could allow definitive treatment of patients to begin sooner, thereby shortening hospital stays.

In many cases, the initial work began in academic laboratories and has moved to biotechnology companies, some of them spun off from labs at such institutions as Harvard and MIT. A survey by Neil A. Holtzman of the congressional Office of Technology Assessment showed that some 50 companies are now using or planning to use probes of human DNA in their research programs.

The genetic diagnosis business is truly in its infancy, however. Both the size of the future market and those who will dominate it are hard to predict.

For the short term, there will be no bonanza in genetic testing. At present, the tests can indicate only whether a second child in a family that already has a child with a given disease will also carry the defective gene. Tests that can screen a large population of pregnant women for a certain disease—thus creating a far larger demand—cannot be devised until the actual genes for the diseases are identified and cloned. That there are 3.3 million live births per year in the United States gives some idea of the potential market for screening.



Margaret Lambert

Orrie Friedman of Collaborative Research: *"We really own chromosome 7."*

Dollar estimates of the future market are entirely speculative; last year Robert S. First, Inc., of White Plains, New York, a health care management consulting firm, predicted that the human genetics market would be $48 million by 1990, while Integrated Genetics of Framingham, Massachusetts, contends in its advertising that sales could reach $1 billion over the next decade.

However distant the real payoff may be, numerous companies are already scrambling to secure a dominant position, reckoning that only a handful of key players will share the fruits of the technology. Consequently, they are adopting novel and widely different strategies to gain a competitive edge. At least one firm is putting its main efforts into developing hundreds of probes for genetic markers, hoping to patent them, on the theory that this strategy will increase the chance of being able to develop proprietary tests for a wide range of diseases. Other companies are throwing their resources into developing tests for a few particular diseases that affect relatively large numbers of people. Still others believe they will gain an advantage not in developing tests but through technological innovations for making the tests rapid and simple to perform.

The DNA probes that are the workhorses of genetic research and diagnosis are radioactively labeled sequences of DNA that can be used to search through the entire genome of a cell to find a desired target sequence. When the probe binds to that sequence because their nucleotides are complementary, the radioactive labeling betrays the presence of the target sequence. The probes are usually random DNA sequences from a human DNA library.

A genetic marker is a bit of DNA that lies near a disease gene that has not been identified. If the marker is consistently inherited by victims of the disease, it signals that the defective gene must be near the marker. Therefore, genetic markers serve as proxies for the hidden genes in diagnostic testing. They also define the region on the chromosome where the gene must be, and narrow the effort to isolate the defective gene itself. Tests for individual diseases are created by locating a series of markers that tightly encompass the suspected disease locus.

Until recently, prenatal diagnostic testing was limited to gross chromosomal abnormalities such as Down's syndrome or disorders like Tay Sachs disease, in which the mutant gene product was known. With DNA probes and genetic markers, however, it is theoretically possible to detect most of the diseases caused by single gene mutations. More than 3000 of these are known, and although some are not uncommon—such as cystic fibrosis, which affects one in 2000 Caucasian children—most are rare.

Ultimately, it may be possible to screen people for genetic predisposition to some common diseases, such as cancer, in which several genes—perhaps entire gene families—may act together and in concert with environmental factors to put certain individuals at higher risk. "This is where business ventures will find their profit," predicts Jerome Donlon of the Food and Drug Administration. Companies already focusing on

this market foresee a great demand for tests to screen employees of entire companies or other large groups. "A lot of people are very interested in this," says Ray White, a geneticist at the University of Utah. "There are two levels: first, you test with markers to define predispositions, and having implicated [certain] genes . . . you study how these genes work. Then new means of intervention will suggest themselves, and you market the drugs you can take to mitigate the predisposition," he said.

One firm building a strategy around predisposition testing is California Biotechnology, Inc., of Mountain View. Scientists are evaluating potential markers for susceptibilities to atherosclerosis, hypertension, and diabetes. Philippe Frossard, project leader of the marker program, says that CalBio scientists are screening about 20 genes known to be involved in lipid transport, which might, because of mutations, play a role in elevated risk for atherosclerosis.

All of the players in the probe game, however, are shooting in the dark with respect to one issue hanging over the entire industry—patents. The initial court decision that life forms were patentable has not yet been refined in terms of what fruits of biotechnology can be protected.

Few claim to be able to predict how patent questions will affect competition in the new field of gene mapping by markers and DNA probes. Most companies are applying for patents on everything in sight—mapping processes, individual probes, methods for enhancing DNA analysis, and so forth. At Collaborative Research of Waltham, Massachusetts, for example, an aggressive patent stance leads chairman and chief executive officer Orrie Friedman to say, "We have 54 markers on chromosome 7. We have mapped it in a way no chromosome has ever been mapped—we really own chromosome 7." Collaborative Research also suggests that it has a dominant proprietary position in testing for cystic fibrosis, because its scientists found the first linked marker on which subsequent research was based and also discovered that the gene was on chromosome 7.

Probes, markers, and genes are moot issues in the view of John Sninsky, head of diagnostic services at Cetus Corporation in Emeryville, California, where work on human diagnostics is under way. "In the past, people have viewed the identification of the gene as the sole patentable resource," he said. "But I think that's incorrect: to have access to making money it's necessary to have, first, access to the probe, and second, the ability to incorporate it in a rapid, sensitive test. We would argue that because of our [test format] system we bring as much to the table as someone who identifies a probe."

It is likewise unclear whether patent protection will be used to try to exclude others from the field or, rather, to use royalties as a major source of income. Mark Goldberg, of Genetics Institute in Cambridge, Massachusetts, points out that a patent dispute between Genentech and Biogen over interferon ended with the two firms cross-licensing each other, saying that made more sense than an expensive legal battle. "One might expect that that is a good paradigm for what might occur in the future," he said.

Nevertheless, patent expectations are a key to the strategy being adopted by Collaborative Research, one of the acknowledged leaders in human DNA probe genetics. The firm has invested heavily in the technology and manpower to develop many random probes and in fact has a bank of more than 500—roughly equal to all probes created elsewhere. The underlying presumption is that if the probes can be patented, having a great number could give the firm an unbeatable head start in developing tests for given diseases.

There is a debate about whether having a probe or a sensitive test system will give a competitive edge.

Scientists at Collaborative Research assert that they are so far ahead in probes that they will also be able to generate a proprietary map of the entire human genome. This will put the company in a position to devise tests for almost any desired disease gene and for multifactorial conditions, they say.

Furthermore, Collaborative Research currently holds an exclusive license on a pending patent covering the basic gene-mapping process, frequently referred to as mapping by restriction fragment length polymorphisms or simply RFLP's. The concept of gene mapping by random linked markers was developed in 1980 by David Botstein of MIT (a member of Collaborative's scientific board), White and Mark Skolnick of the University of Utah, and Ronald Davis of Stanford.

Stanford filed for the patent on behalf of the institutions, which agreed to split the royalties. More than 5 years later, the patent still has not been issued. Meanwhile, Collaborative Research acquired an exclusive license under an agreement that is intended to cover the basic process of gene mapping by linked genetic markers.

Bernadette Alford, director of licensing and patents for Collaborative Research, says, "We feel we would really have a dominant position in any type of diagnostic testing using RFLP's." She adds that the company does not intend to exclude others from the field, but wants to reap economic rewards in the form of licensing fees. Analysts say that pressure from commercial and academic researchers would probably be exerted to keep licensing fees low so as not to hamper progress.

Friedman ultimately views Collaborative becoming a center of molecular genetics, having the expertise to devise tests and a laboratory to carry them out (the laboratory was established this year), and perhaps forging a relationship with a pharmaceutical company to develop therapies. But whether this plan can be sold to investors remains to be seen, and if it requires gaining a unique position vis-à-vis patents, some observers are skeptical.

"I don't understand Collaborative's approach," says White, who formerly had a scientific relationship with the firm. "By competing with universities they put a lot of money into something the academics are going to get hold of anyway . . . . It's not possible to protect a map of a chromosome."

He noted also that although Collaborative scientists, in a joint project with researcher from the Hospital for Sick Children in Toronto, found the first marker for cystic fibrosis and determined which chromosome it is on, they gained little advantage.

"Their commercial position was blown out of the water when Robert Williamson [of St. Mary's Hospital Medical School, London] and we each found closer markers," said White, who also said there is accumulating evidence that two markers in the public domain are close enough for devising a test.

It has been widely pointed out that patented markers may not mean much. As soon as one firm announces that it has found a marker using its proprietary probe, others are sure to find closer and better ones. Some analysts also say that the bulk of useful markers will come out of academic laboratories all over the world, making it difficult for any one company to corner the probe market.

A close rival of Collaborative Research, Integrated Genetics, was founded by several researchers including David Housman of MIT and James Gusella of the Massachusetts General Hospital, both of whom were involved in work leading to the discovery by Gusella of the first genetic marker for Hun-

tington's disease. The company has a large effort in DNA probes for detecting food contamination, a program in therapeutic DNA-based products, and one in fertility hormones.

In human genetics, Integrated Genetics takes a different tack from Collaborative Research: "Collaborative started out to make tons of polymorphisms (probes), while we decided on a more targeted strategy—creating a research program dedicated to a specific disease" like cystic fibrosis, says Katherine Klinger, senior scientist, who adds that while the company does develop its own probes, it also uses those given by other researchers or licensed at various fees.

"Our plan has been to isolate probes for CF [cystic fibrosis] and then go disease by disease," says Patrick Connoy, vice president for sales and marketing. While Collaborative Research spreads its resources across the genome looking for probes, he said, Integrated Genetics will focus its manpower on a handful of diseases with the aim of cloning the genes and selling diagnostic tests, then moving on to other diseases. Integrated's plans at present include cystic fibrosis, Huntington's disease, adult polycystic kidney disease, and factor IX deficiency.

Both companies have established reference laboratories and are advertising them in the hope of gaining a competitive edge that will later allow them to profit from wider scale testing such as pregnancy screening. At present, most prenatal testing is still conducted at medical centers and universities.

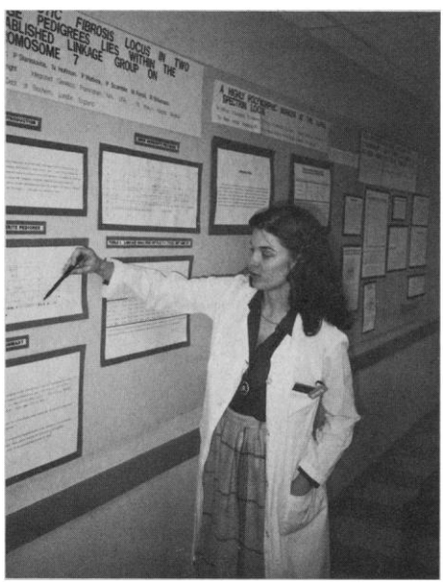
However, as an example of how a new technology or marketing arrangement can transform this emerging field almost overnight, Cetus has recently emerged as perhaps the strongest entity by virtue of a new method of DNA analysis.

Cetus scientists this year revealed a technique for amplifying desired sequences in a DNA sample by as much as a millionfold, making them that much easier to detect. "It reduces the complexity of the DNA so you can use shorter oligonucleotides (laboratory-built probes)," and there are many other advantages, says Sninsky, the diagnostics director. With this technique in hand, the company is searching for diseases and disease predispositions for which tests can be made.

Robert Kupor, a biotechnology analyst with Cable, Howse, and Ragan of Seattle, says, "Cetus's seems to me to be ahead of anyone else." He says the company could be making $200 million a year by 1990 from the technology. Cetus's plans to license its format for testing and also market, in 1988, a machine for automating the tests.

"Companies like Collaborative and Integrated will need a format to get the price of their tests down," says Kupor. "What Cetus will hope to do is allow the companies to format their tests so that they can be put into a Cetus machine." Cetus's probe-based diagnostics work is being undertaken in a joint venture with Eastman Kodak Company.

In addition to Cetus and California Biotech, the industry giant Genentech is exploring screening for predisposition to common diseases, according to Angelo M. Scanu, professor of medicine at the University of Chicago. Scanu says that he has identified a marker for a low-density lipoprotein, called LPa, which is found in 10 to 20% of the population. Even patients who have mild total cholesterol elevations have a greatly increased risk of cardiovascular disease, said Scanu, adding that Genentech is working toward a simple test for screening.



Katherine Klinger: *Integrated Genetics is focusing on specific diseases.*

While such companies as these envision sharing in a large future market, some smaller firms are seeking niches for specific applications of DNA probes. One such is Lifecodes, Inc., of Elmsford, New York. It is specializing in paternity testing, with an established market of 60,000 tests a year to establish the biological father for child support enforcement in New York State, and to determine identity in forensics cases—for example, matching the DNA of sperm from rape victims with that of suspected rapists to help determine guilt.

Helen Donis-Keller, director of human genetics at Collaborative Research, commented, "This marker technology opens up a new future for medicine. Using it, we will be able to follow any inherited trait from generation to generation. We will also be able to use these markers to find the gene or genes responsible for many genetic diseases—someday, perhaps, we will have found them all. And when that happens, we will be well on our way to ridding society of much of the suffering caused by disease."

Still, there are some who are taking a concerned view of this rush to commercialization. Heretofore, the complexities and rigorous quality requirements of genetic testing have mainly been dealt with in academic centers. Not only is assurance of accuracy a must. Predictive tests generally do not yield simple answers, but rather produce statistical probabilities of patients or fetuses being afflicted. The interpretation of these tests and the genetic counseling of families at risk require great experience and commitment.

These and other issues were raised recently at a meeting in Albany, New York, sponsored by the New York State Health Department. Department officials noted that the technology is so new that the state has no mechanism for licensing DNA probe labs.

The most pointed expression of concern came from Holtzman of OTA. At present, he said, companies are very sensitive to the problems of accurate diagnosis, but "if every genetics center around the country—academic or commercial—tries to set up probe testing, there are going to be difficulties."

The tests are not easy to perform in the best of laboratories, he said, but if they become the province of general medical labs, "reliability is sure to suffer" without adequate quality control. He enumerated problems such as incomplete DNA digestions, faulty hybridizations, mislabeling, and contamination.

Another worry, Holtzman said, is that given the tendency for tests to be performed in doctors' offices, the tests may be sold widely in kits "and then you open up a whole set of problems in reliability and interpretation."

Holtzman and others at the meeting also said they feared that testing would be carried out in situations where thorough genetic counseling is not available, a problem that could lead to badly thought-out decisions by people under stress. Donlon of FDA raised another question: "How will we validate these tests when there are no other assays available?"

Such questions will prove weighty issues for the FDA, he said, and concluded, "This technology is opening up new testing possibilities and creating a revolution in the field of medical genetics. It will be a challenge." ■ RICHARD SALTUS

Richard Saltus is a reporter for the Boston Globe.