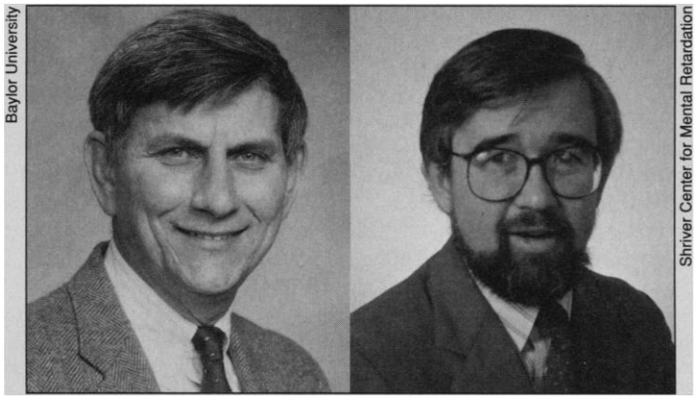
Cystic Fibrosis Pilot Projects Go Begging

Everyone agrees that trials to test the feasibility of widespread cystic fibrosis screening are needed. But where's the money?

SOON AFTER THE CYSTIC FIBROSIS GENE WAS discovered in the summer of 1989, a heated debate erupted on whether and when to begin widespread population screening for the disease, the most common fatal genetic disorder among Caucasians. There was one point, however, that everyone endorsed: Pilot projects were urgently needed to determine how best to deliver the test and what the pitfalls might be.

Now, more than a year later, pilot projects are under way in England and Canada, but nothing is even on the drawing boards in the United States. The private and federal groups likely to fund such work are tossing it around like a hot potato, in part because no one is flush with funds at the moment—and pilot studies can be expensive—and in part because of political skittishness over abortion, with which genetic screening is inevitably linked.



Ante up. *Geneticists Tom Caskey and Philip Reilly want NIH to foot the bill for pilot studies.*

And that is deeply troubling to many geneticists, like Francis Collins of the University of Michigan, one of the discoverers of the gene, who see cystic fibrosis screening as a prototype for other genetic tests sure to come. In addition to the many questions that accompany any genetic screening effort, such as how to educate and counsel the population, cystic fibrosis brings a troubling new one. The problem is the imperfect sensitivity of the existing test, which allows the unequivocal detection of only about half the couples at risk of having a child with the disease (also see *Science*, 5 January, p. 17).

For that reason, both the American Society of Human Genetics and an expert committee of the National Institutes of Health issued guidelines last March advising against mass screening until the test is capable of detecting 95% of those who carry the defective gene, and calling for pilot studies in the interim.

While the 95% test remains elusive, the detection rate has improved, and sentiment appears to be shifting in favor of more widespread testing. Already, more and more tests are being conducted around the country. And at least one maverick group of doctors has embarked on a controversial program to screen the general population—all without the guidance that pilot studies could offer.

What happened to the studies? The most likely source of funds, the Cystic Fibrosis Foundation, took itself out of the running right away. "We stay away from screening 100%," admits Robert Beall, executive vice president and medical director at the foundation, who says its mission is to find a treatment and cure for the disease—not to prevent it. "For us to invest in issues outside our main mission would take funds away from the work we do."

Beall denies that abortion is an issue, but several people close to foundation officials say it played a major role in what has been a wrenching decision for them. The officials were reportedly afraid that by supporting screening—and thus, implicitly, abortion of affected fetuses—they would risk losing the financial contributions that make their research possible.

For a while, it looked as if NIH might come up with the funds for pilot studies, but so far, scientists have gotten what they think is the runaround. Judy Fradkin of the National Institute of Diabetes, Digestive, and Kidney Diseases, which has provided the lion's share of NIH funding for cystic fibrosis research, says that in a time of limited funds, pilot projects are "not our highest priority." She suggests people direct their funding pleas and grant applications to the genome office at NIH, which has set aside 3% of its budget for research on ethical, legal, and social questions.

Too clinical, responds Elke Jordan, deputy director of the genome office, who notes that NIH typically does not fund this type of research. Nonetheless, she says, the genome office may pick up part of the tab for such studies, but not all. Jordan bridles at the notion that NIH is passing the buck, especially since her office is actively trying to locate other funds for pilot studies. Others speculate, however, that at a time when NIH remains without a permanent director, institute heads are leery of entering into anything that smells of abortion.

All of this earned both NIH and the Cystic Fibrosis Foundation few kind words at a meeting on genetic screening in early November at the Banbury Center at Cold Spring Harbor Laboratory. Geneticist Tom Caskey of Baylor College of Medicine, one of the organizers of the meeting, berated both NIH and the Cystic Fibrosis Foundation for "foot-dragging." The first time NIH "screwed up" the foundation came in with funds, said Caskey, referring to an episode several years ago when NIH stopped supporting research to find the cystic fibrosis gene, under the mistaken impression that it had been found. But this time, he said, the foundation is nowhere to be seen.

As for the feds, "NIH loved cystic fibrosis screening a year ago," said Caskey, referring to the publicity and press releases surrounding the March workshop NIH convened. "But then they walked away from it," setting aside no special funds for pilot studies and, indeed, turning down applications. Says Caskey: "We are in a mess."

Caskey and the other geneticists at the Banbury meeting were hardly mollified when Eric Juengst of the NIH genome office offered what he thought was at least a partial palliative. He reported that the genome office has identified a "hot prospect" to pick up the tab for the clinical aspects of pilot studies: the Agency for Health Care Policy Research, a new Public Health Service agency with a budget of just $117 million, compared to NIH's $8.3 billion.

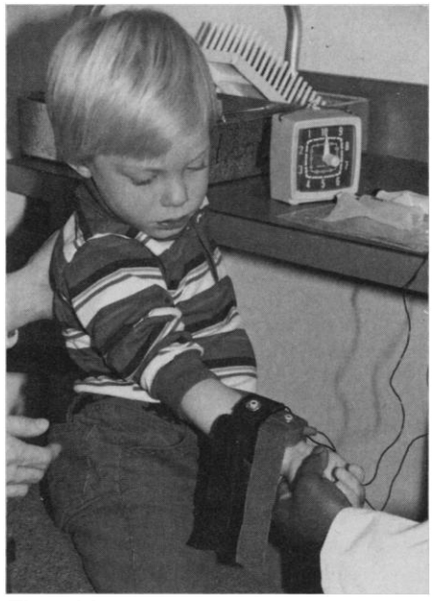
But the new health care research agency is not yet leaping in to fill the void. "Our budget is not NIH's; there are limits to what we can do," Jacqueline Bestman, assistant to the director, told *Science*. Funding pilot projects is "not out of the question, but it is not in our portfolio at this time," she said.

And at this point, time is running out, at least for the ambitious studies geneticists

originally had in mind, says Philip Reilly, a geneticist and lawyer at the Shriver Center for Mental Retardation in Waltham, Massachusetts. "We should be 6 months in," Reilly says. "If we started in June 1991, ran a 2-year study, and published in January 1994, it would be too late. Once we hit the 90% detection level, then it won't matter if we have pilot projects or not. The cat will be out of the bag"—and testing will already be widespread. Instead, Reilly is pushing for smaller studies, addressing such critical issues as how much anxiety the test produces, that could be done quickly when they still might have some impact.

Meanwhile, more and more couples are being tested around the country. A handful of companies are now each testing anywhere from 10 to perhaps 40 or 50 people a week, at $125 to $225 per sample. At Baylor College of Medicine, the biggest academic testing center, Arthur Beaudet expects to test 600 people this year, three times more than last year. So far, academic centers and companies alike say they are still testing mostly those couples with a family history of cystic fibrosis—and not the general population—in keeping with the guidelines the NIH committee promulgated last March.

But it is not clear how long those guidelines will hold sway—or, in fact, whether they should. The reason? It is no longer certain that the test's detection rate will ever reach the magical 95% level (see box). As that reality sinks in, withholding the test indefinitely is beginning to seem less and less tenable, at least to some.



Cystic Fibrosis Foundation

The old way. *A child receives a sweat test to determine if he has cystic fibrosis.*

Reilly said as much at the American Society of Human Genetics meeting in Cincinnati in October. One year earlier the genetics society issued a statement that held that cystic fibrosis screening was not the standard of care—in other words, physicians should not be held liable if they did not offer the test and a couple had a child with cystic fibrosis. But this year Reilly, who wrote that sentence in the earlier statement, delivered a very different message. He told the crowd that once the test reaches the 90% detection level, which researchers think it may soon, the courts are likely to consider cystic fibrosis testing standard care. His message, in short, was inform *all* patients about the test or risk a lawsuit and some hefty damages.

No sooner had Reilly finished his talk than Michael Kaback, president of the American Society of Human Genetics, exploded, lambasting Reilly for telling the crowd, in so many words, to begin offering the test, which Kaback still thinks has the potential to cause great harm. But his view seems to be increasingly in the minority. "Attitudes are shifting," says Beaudet. "Maybe it is not our business to decide not to offer the test."

Indeed, one private genetics practice has already begun doing what many others seem to be contemplating. Joseph Schulman, director of the Genetics and IVF Institute in Fairfax, Virginia, is offering prenatal testing for cystic fibrosis to every one of the 400 or so couples that comes through his clinic each month. Since February, about one-fourth, or 900 couples, have agreed to take the test, which they have to pay for themselves, says Schulman. He adds that the clinic intends to begin offering the test to the general population.

Schulman's screening was instantly condemned by some of his colleagues—especially because his group, unlike the DNA testing companies, both orders and performs the test, thereby profiting from it. While that is common practice for many procedures, like a standard blood count, it just hasn't happened yet in cystic fibrosis testing. "This is not just appearance of conflict of interest but the reality," said Norman Fost of the University of Wisconsin at the Banbury meeting.

Beaudet, however, is not so quick to condemn the group. "To say Schulman is at one end of the spectrum does not mean he is wrong. You might find in a few more months that most geneticists will be doing what he is doing."

Meanwhile, Schulman and his colleagues report that so far their screening has caused no undue anxiety—and no abortions—in couples who learned their children would be carriers. (No cystic fibrosis cases were detected.) Until the federally funded pilot projects get off the ground, if they ever do, most of the information about cystic fibrosis screening may come from small, more anecdotal studies like Schulman's.

■ LESLIE ROBERTS

CF Gene Proves Uncooperative

Since the cystic fibrosis gene was discovered more than a year ago, some 80 labs around the world have been furiously scouring its DNA, seeking out additional defects. Without them, geneticists say, the cystic fibrosis test is not sensitive enough for widespread carrier screening.

The problem with the existing test is that the defect discovered in the summer of 1989 is present in only about 70% of the individuals who carry the disease gene; the other carriers have different mutations in the same gene. And that means that a DNA test based solely on the original mutation would identify just 70% of the carriers, and thus only half of the couples at risk of having a child with cystic fibrosis. What's more, in a substantial number of the couples tested, one partner would test positive and one negative—and there would be no way to tell whether the person with a negative test in fact harbored the defective gene. Thus the call for a voluntary moratorium on mass screening until a more accurate test, capable of detecting 95% of all carriers, became available (*Science*, 16 March, p. 1297).

When the original gene defect was discovered, geneticists optimistically predicted that there would be no more than a half-dozen to a dozen additional mutations and that they would find them within a year, making possible an extremely sensitive test. But so far they have turned up more than 60—none of which occurs with any notable frequency. In fact, many mutations seem to occur in just one person. "As more time goes by and we don't bump into any more frequent mutations, you start to wonder if we ever will," says Francis Collins of the University of Michigan, one of the discovers of the original defect.

Meanwhile, by also screening for a few of the additional mutations that occur in 1 to 3% of carriers, Arthur Beaudet of Baylor College of Medicine has achieved a detection rate of 80 to 85% in the general population. Beaudet, for one, is optimistic that the detection rate may reach 90% in the next 6 months or so. But among many other geneticists, hopes are fading of reaching 95% detection any time soon, at least in an affordable test. ■ L.R.