RESEARCH

Genes Now Tell Doctors Secrets They Can't Utter

By GINA KOLATA AUG. 25, 2012

Dr. Arul Chinnaiyan stared at a printout of gene sequences from a man with cancer, a subject in one of his studies. There, along with the man's cancer genes, was something unexpected — genes of the virus that causes AIDS.

It could have been a sign that the man was infected with H.I.V.; the only way to tell was further testing. But Dr. Chinnaiyan, who leads the Center for Translational Pathology at the University of Michigan, was not able to suggest that to the patient, who had donated his cells on the condition that he remain anonymous.

In laboratories around the world, genetic researchers using tools that are ever more sophisticated to peer into the DNA of cells are increasingly finding things they were not looking for, including information that could make a big difference to an anonymous donor.

The question of how, when and whether to return genetic results to study subjects or their families "is one of the thorniest current challenges in clinical research," said Dr. Francis Collins, the director of the National Institutes of Health. "We are living in an awkward interval where our ability to capture the information

The federal government is hurrying to develop policy options. It has made the issue a priority, holding meetings and workshops and spending millions of dollars on research on how to deal with questions unique to this new genomics era.

The quandaries arise from the conditions that medical research studies typically set out. Volunteers usually sign forms saying that they agree only to provide tissue samples, and that they will not be contacted. Only now have some studies started asking the participants whether they want to be contacted, but that leads to more questions: What sort of information should they get? What if the person dies before the study is completed?

The complications are procedural as well as ethical. Often, the research labs that make the surprise discoveries are not certified to provide clinical information to patients. The consent forms the patients signed were approved by ethics boards, which would have to approve any changes to the agreements — if the patients could even be found.

Sometimes the findings indicate that unexpected treatments might help. In a newly published federal study of 224 gene sequences of colon cancers, for example, researchers found genetic changes in 5 percent that were the same as changes in breast cancer patients whose prognosis is drastically improved with a drug, Herceptin. About 15 percent had a particular gene mutation that is common in melanoma. Once again, there is a drug, approved for melanoma, that might help. But under the rules of the study, none of the research subjects could ever know.

Other times the findings indicate that the study subjects or their relatives who might have the same genes are at risk for diseases they had not considered. For example, researchers at the Mayo Clinic in Rochester, Minn., found genes predisposing patients to melanoma in cells of people in a pancreatic cancer study — but most of those patients had died, and their consent forms did not say anything about contacting relatives.

One of the first cases came a decade ago, just as the new age of genetics was beginning. A young woman with a strong family history of breast and ovarian cancer

the risk of breast cancer. But the woman, terrified by her family history, also intended to have her breasts removed prophylactically.

Her consent form said she would not be contacted by the researchers. Consent forms are typically written this way because the purpose of such studies is not to provide medical care but to gain new insights. The researchers are not the patients' doctors.

But in this case, the researchers happened to know about the woman's plan, and they also knew that their study indicated that she did not have her family's breast cancer gene. They were horrified.

"We couldn't sit back and let this woman have her healthy breasts cut off," said Barbara B. Biesecker, the director of the genetic counseling program at the National Human Genome Research Institute, part of the National Institutes of Health. After consulting the university's lawyer and ethics committee, the researchers decided they had to breach the consent stipulations and offer the results to the young woman and anyone else in her family who wanted to know if they were likely to have the gene mutation discovered in the study. The entire family — about a dozen people — wanted to know. One by one, they went into a room to be told their result.

"It was a heavy and intense experience," Dr. Biesecker recalled.

Around the same time, Dr. Gail Jarvik, now a professor of medicine and genome science at the University of Washington, had a similar experience. But her story had a very different ending.

She was an investigator in a study of genes unrelated to breast cancer when the study researchers noticed that members of one family had a breast cancer gene. But because the consent form, which was not from the University of Washington, said no results would be returned, the investigators never told them, arguing that their hands were tied. The researchers said an ethics board — not they — made the rules.

Dr. Jarvik argued that they should have tried to persuade the ethics board. But,

Such ethical quandaries grow more immediate year by year as genome sequencing gets cheaper and easier. More studies include gene sequencing and look at the entire genome instead of just one or two genes. Yet while some findings are clear-cut — a gene for colon cancer, for example, will greatly increase the disease risk in anyone who inherits it — more often the significance of a genetic change is not so clear. Or, even if it is, there is nothing to be done.

Researchers are divided on what counts as an important finding. Some say it has to suggest prevention or treatment. Others say it can suggest a clinical trial or an experimental drug. Then there is the question of what to do if the genetic findings only sometimes lead to bad outcomes and there is nothing to do to prevent them.

“If you are a Ph.D. in a lab in Oklahoma and think you made a discovery using a sample from 15 years ago from a subject in California, what exactly are you supposed to do with that?” asked Dr. Robert C. Green, an associate professor of medicine at Harvard. “Are you supposed to somehow track the sample back?”

Then there are the consent forms saying that no one would ever contact the subjects.

“If you go back to them and ask them to re-consent, you are telling them something is there,” Dr. Green said. “There is a certain kind of participant who doesn’t want to know,” he added, and if a researcher contacts study subjects, “you are kind of invalidating the contract.”

Other questions involve the lab that did the analysis. All labs providing clinical results to patients must have certification ensuring that they follow practices making it more likely that their results are accurate and reproducible. But most research labs lack this certification, and some of the latest genetic tests are so new that there are no certification standards for them.

“I find it really hard to defend the notion that we are not going to give you something back because it was not done” in a certified lab, “even though we are 99 percent certain it is correct,” Dr. Jarvik said.

Gloria M. Petersen, a genetic epidemiologist at the Mayo Clinic, and her colleagues ran into a disclosure problem in a study of genes that predispose people to pancreatic cancer. The 2,000 study patients had signed consents indicating whether they wanted to know about research findings that might be important to them. But the forms did not ask about sharing findings that might be important to their families, or about what the researchers should do if they discovered important information after the patients were dead.

Seventy-three of the study patients, almost all of whom are now dead, had one of three clinically important mutations. One predisposed them mostly to melanoma but also to pancreatic cancer. A second predisposed them primarily to breast and ovarian cancer. The third, a cystic fibrosis gene, can increase the risk of pancreatic cancer and can also be important in family planning. If a man and a woman each have this gene, they have a one-in-four chance of having a child with the disease.

When it comes to the family members, “I don’t know what my obligation is,” Dr. Petersen said. “There is an incredible burden to track down the relatives. Whose information is it, and who has a right to that information?”

Dr. Petersen, along with Barbara Koenig, a professor of medical anthropology and bioethics at the University of California, San Francisco, and Susan M. Wolf, a professor of law, medicine and public policy at the University of Minnesota, got a federal grant to study the effects of offering to return the genetic results to the families of those 73 patients. The questions involved are tricky, Dr. Koenig said. Finding patients and their families can be expensive, and labs do not have money set aside for it. How would you find them? Even if they were found, whom would you tell? What if there had been a divorce, or if family members were estranged?

“My gut feeling is that there is a moral obligation to return results,” Dr. Koenig said. “But that comes at an enormous cost. If you were in a study 20 years ago, where does my obligation end?”

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