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Using Gene Tests to Customize Medical Treatment

By GINA KOLATA

Warren Wegele is on the front line of a medical revolution.

After doing a simple blood test recently, doctors at the University of Cincinnati Medical Center told Mr. Wegele, a 65-year-old former salesman for air compressor companies, that he had inherited a tiny alteration in one of his genes. A certain chemical unit out of the string of three billion that make up the mass of DNA in his cells is different from the norm.

The alteration -- found in 5 percent of the population -- would normally be of no more medical significance to Mr. Wegele (pronounced WEG-lee) than his black hair or burly physique. But it translated into a potential medical catastrophe for Mr. Wegele when he became ill with congestive heart failure, a disease in which the heart muscle no longer contracts vigorously. On average, patients with the condition live 5 years after they become ill; some live 10 years or more.

But people with anomalies like Mr. Wegele's altered gene, doctors told him, usually live only one to two years. For these people, the drugs used to treat the disease may be of little help.

"I don't accept it," Mr. Wegele said of the bad news doctors gave him about his gene, which directs heart cells to make a crucial protein. After all, he argued, as he lay in his hospital bed, "I've never really gotten ill, and I've always recovered from everything instantly."

But Mr. Wegele's former vigor was beside the point. Clearly ill, he had spent weeks in the hospital, growing sicker by the day, waiting for a heart to become available for a transplant -- the only way, his doctors said, to save his life.

The revolutionary new genetics that predicted Mr. Wegele's dire circumstances is not about genes that confer generally good health or health that is generally poor. Instead, it is about a collection of common single-molecule variations in genetic material that are normally no more important than having curly or straight hair or brown or blue eyes, but might be revealing when people become ill.

Scientists believe humans have hundreds of thousands of these genetic variations, and drug companies are avidly searching for them, convinced that they can use collections of them to identify patients who will benefit from drugs, patients who will not, and patients who will suffer troubling side effects.

Eventually, they say, this research will lead them into an era of tailor-made medicine.

So far, testing for such genetic variants is being done only at a few medical centers as part of experimental trials. Experts predict a gradual increase in such testing as the roster of variations is compiled and research accelerates. They predict that the first personalized drug prescriptions will appear in a few years and many more will roll out over the next two decades.

At first, the advanced genetic testing will probably be used for refining drugs for the more common diseases like asthma, arthritis, heart disease, high blood pressure and migraines. Eventually, experts say, it could be applied to virtually any drug for any disease.

Drug prices could increase, some drug company executives say, but they add that drugs will be so much more effective that they will be worth more to patients.

Of course, optimistic predictions of scientists and drug companies can go awry, and until the revolution in pharmacology takes place, it is hard to know if the glowing predictions are accurate. So far, only a relatively few genetic variants have been found and only a small number of these have been shown to have medical consequences.

In Mr. Wegele's case, there was no good drug to slow his disease. But that did not mean he had not been helped. Based on their data from a continuing study that now includes about 500 patients with congestive heart failure, doctors at the University of Cincinnati hospital said that the only long-term hope for people with Mr. Wegele's genetic variant was a heart transplant.

"We test everyone who has congestive heart failure," said Dr. Stephen Liggett, a lung specialist and molecular geneticist at the

University of Cincinnati College of Medicine, who discovered the genetic variant and its effects on congestive heart failure. Dr. Liggett said it was his opinion that those who had the genetic variation, like Mr. Wegele, "should be put on the transplant list early and they should have more aggressive drug therapy."

On Dec. 9, Mr. Wegele received a new heart. A week later, Dr. Liggett said, Mr. Wegele was well enough to be sent home.

The Scientists

From Impossible Task To Reasonable Goal

Five years ago, when he was giving a technical talk to scientists, Dr. Eric Lander had a eureka moment. Dr. Lander, who is director of the Center for Genome Research at the Whitehead Institute in Boston, had assumed that it would be hopeless to even dream of finding the common variants in human genes. Gene alterations -- single chemical changes -- occur by accident, at random. Those with an immediate effect on health or fertility would be retained or eliminated by evolution.

The other alterations would be neutral -- they would ordinarily make no difference to the person -- and so they would slowly become common as they were passed from generation to generation.

With about 100,000 human genes and six billion people on earth, the number of common variations could be enormous. But, Dr. Lander realized, the human race numbered just 10,000 to 100,000 people as recently as 7,000 generations ago and a population that small would have only a modest number of common genetic variants, perhaps a few hundred thousand.

"There hasn't been enough time for the common variants to build up," Dr. Lander said. For each gene, there might be two, or three, common variations at one or two positions in the gene sequence, not hundreds.

"It becomes a finite problem," Dr. Lander said. "It is within reach."

That insight converted him into one of the pioneers in the search for genetic variants that can predict individual differences in responses to illness and responses to drugs, a field known as pharmacogenetics.

Around the same time Dr. Lander was realizing that each gene might have just a few variants, Dr. Liggett, then a researcher at Duke University, was starting to see what such variants might mean for patients.

Dr. Liggett was intrigued by one particular gene, the beta-2 adrenergic receptor gene. It directs cells to make a protein that helps relax muscles in the airways of the lungs and contract muscles in the heart. Drugs for asthma attach themselves to the protein, setting off a cascade of biochemical events inside the cells that makes the airways dilate. Drugs for congestive heart failure also attach themselves to the protein, this time making heart muscles contract.

In studies with cells grown in the laboratory, Dr. Liggett discovered that the gene that codes for production of the beta-2 adrenergic receptor protein seemed exquisitely tuned by its structure. A change in just a single chemical along the gene's length could make the protein work slightly better, or slightly worse.

The next step was to find out if this could occur in humans.

Dr. Liggett and his colleagues recruited 100 healthy people and began deciphering the chemical sequence of each person's beta adrenergic receptor gene. After 18 months, he got his answer. There were three different variants of the gene. All three worked fine.

Nonetheless, Dr. Liggett's mind raced. Maybe this was why some people respond better than others to asthma drugs. Maybe it was why some people taking asthma drugs quickly become resistant to them and others did not. Maybe it was also tied to the way patients with congestive heart failure responded to drugs.

"A lot of people told me that what we had found was unimportant," Dr. Liggett said. "They were wrong."

Last year, in a paper in *The Journal of Clinical Investigations*, Dr. Liggett and his colleagues showed how the genetic variants affected disease prognosis in congestive heart failure. Reporting on tests of 259 patients who had come to the University of Cincinnati to be evaluated for possible heart transplants, the researchers found that those with one particular beta-2 adrenergic receptor gene variant did far worse than those with another. A third group was in the middle.

Within 100 days after they arrived at the hospital, about 60 percent of the patients with an isoleucine amino acid at position 164 in the protein chain were dead or required a heart transplant. That is the variant that Mr. Wegele has.

Patients with a different amino acid, threonine, at position 164, had a much better outcome. About 95 percent of them were alive after 100 days without having had a heart transplant, and half were still alive 900 days after they first arrived at the hospital.

Other changes in the gene appear to be important in asthma.

In a recent small study conducted at the University of Tennessee at Memphis, Dr. Julie A. Johnson, Dr. John J. Lima and their colleagues found that asthma patients who inherited from both parents the amino acid arginine in position 16 of the beta-2 adrenergic receptor protein responded best to the popular asthma drug albuterol. The drug increased the amount of air they could expel from their lungs by 18 percent. Those who inherited from either parent the chemical glycine in that position had just a 4.9 percent increase in the air they expelled.

"We've always known that some people respond better to albuterol," Dr. Liggett said. "But we've never known why."

Now the challenge is to tailor drug treatments to help those who have genetic variants that spell a poor prognosis.

"That," said Dr. Liggett, "is the key to pharmacogenetics."

The Drug Companies First-Time Step In Joint Research

Hidden in the rolling countryside near Hopewell, N.J., in a cluster of brick buildings once owned by Mobil Oil is Bristol-Myers Squibb's budding center of pharmacogenomics research. There, in echoing offices still under construction, Dr. Elliott Sigal makes bold plans to expand his staff and investments in what he believes will be the future of the drug industry.

When executives like Dr. Sigal look at the pharmaceutical industry, they groan. One out of 7,500 compounds that looks promising in the laboratory actually gets to the market. Only 3 out of 10 that are marketed make any money for the company.

"Our attrition rate is a plague for the industry," Dr. Sigal said, referring to the many drugs that fail.

Typically, said Dr. Sigal, who is Bristol-Myer's senior vice president for early discovery and applied technology, major drug companies introduce one innovative drug into the market each year -- if they are lucky. For many drugs, he added, only half of the patients who take them respond.

Some drugs are worse than that. People with conditions like high blood pressure, for example, often find themselves trying one drug after another before they find a medication that works for them.

Other drugs are rarely used because they cause side effects in a small proportion of patients.

For example, a drug like Glaxo Wellcome's Lamictal, which is used to treat epilepsy, can cause itching and rashes. It can only be used by patients whose doctors are willing to start with a small dose and gradually increase it over a period of months, watching to see if a rash develops.

"When most general practitioners see that a drug needs dose escalation, they use something else," said Dr. Allen Roses, a neurologist who is vice president worldwide and director of genetics at Glaxo Wellcome P.L.C. "But it's a great drug."

Dr. Roses and others emphasize that if genetic variants could be used to identify who would respond to a drug and who would have side effects, the benefits for companies and patients would be obvious. Companies could sell more drugs, more efficiently, by marketing them to those who would be helped. And patients would get drugs that worked for them.

For companies like Glaxo Wellcome and Bristol-Myers Squibb, as well as Pfizer, the path is clear. Last April, they and seven other large drug companies joined forces with the Wellcome Trust, a medical research charity, and several leading academic centers, to compare human DNA segments and find the places where variations occur. The companies will use these variations, called single nucleotide polymorphisms, or SNPs, and pronounced "snips," to try to develop the precisely targeted drugs of the future. Their goal is to identify 300,000 such landmarks along the human DNA within two years and make the results public.

On Nov. 21, the group, called the SNP Consortium, published on the Internet its first group of SNP's, identifying 2,279 of them and describing their precise sites on human chromosomes.

But more is involved than just finding SNP's. Companies are also worried about the bottom line: How much will it cost to find these alterations in genes?

Today, it costs \$150 or more to identify each of a person's S.N.P.'s, said Dr. B. Michael Silber, who directs pharmacogenetics research at Pfizer. The goal, he said, is to get the price down to pennies, which he called feasible.

Even a man who describes himself as "leading the way in caution" is convinced that SNP analyses will become cheap enough to be useful. Dr. Paul Spence, the executive director of biotechnology for Searle, the pharmaceutical division of Monsanto, said that before he committed himself to SNP analyses, he actually sat down with pen and paper and worked out the economics. Like Dr. Spence, he concluded that cost would not be an obstacle for long.

As for Dr. Roses of Glaxo Wellcome, as early as September of 1997, he persuaded his company to begin storing DNA samples from every patient in most of its drug studies. The idea is that when the SNP's are found, the company can go back and ask: What patterns of these molecular markers correlate with what sort of drug responses? If one pattern is associated with a drug's efficacy and another with bad side effects, the company would consider marketing the drug only to those with the pattern that predicts a good response.

To protect patients' privacy, Dr. Roses said, their names and identifying features are not stored with their DNA.

Glaxo Wellcome plans to enter the pharmacogenetics market with a drug that is already on the market, offering patients a SNP test before they take the drug to see if they are likely to respond. Then the company plans to move on and use the SNP profiles as part of drug development. In a few years, drug company executives predict, SNP tests will be available for several drugs and several diseases. Eventually, most drugs will be sold with a SNP test, companies say.

Companies expect to use a "SNP chip" for testing. It is a device that can be used to scan a sample of DNA for specific genetic sequences or anomalies.

In the future, drug company executives predict, SNP research will reward them with hundreds of new drugs, including many that will be unlike any on the market today. With that in mind, Dr. Sigal said, his company has a new business goal. Rather than settling for the current pattern of one entirely new drug on the market each year, the company aims to have three.

"Many companies see this as the way of the future," Dr. Sigal said.

The Ethics Discriminatory Risks In Genetic Testing

Mention genes and diseases to many ethicists and they will see a dark side to a bright future. Will people be getting information about their medical conditions that they would rather not know? Can their privacy be protected?

Few are more acutely aware of these problems than Dr. Francis Collins, the director of the National Human Genome Research Institute, the federal effort to map the human genes. From its inception, the genome project has had ethicists as consultants, and it has had to answer piercing questions about the consequences of unveiling what could be intimate genetic information.

While Dr. Collins is excited by the prospect of pharmacogenetics, he sees situations in which it could raise privacy problems. Knowing if someone will respond to a drug, or have a side effect, can tell something about that person's susceptibility to disease.

For example, scientists recently reported that a SNP pattern in a cholesterol-metabolizing gene determined who would respond to the cholesterol lowering drug pravastatin. But the people who respond to pravastatin are also the ones who will have the worst prognosis if they do not get their cholesterol levels down. Insurers might use that genetic information to deny or limit coverage.

"You won't be able to separate the reason you did the test from the response to it," Dr. Collins said.

The solution, he added, is to pass effective laws to prevent genetic discrimination. And, he said, "We are pretty close to seeing that come to pass."

Although genetics always gives rise to ethical concerns, the debate over pharmacogenetics has so far been muted, with even some longtime critics of genetic testing saying that they think it will be a blessing to doctors and patients.

"I'm all for the research," said Dr. Michael Kaback, a geneticist at the University of California in San Diego, who has often criticized genetic testing. "I think it's great."

His main concern, he said, is that companies will promise too much too soon, turning the public bitter and cynical. "Then a whiplash occurs and you end up curtailing progress," Dr. Kaback said.

Dr. Roses noted that the pharmacogenetics approach might not provide people with information about disease susceptibility or their medical futures. While a genetic variant may make a difference in whether a person with asthma, for example, responds to albuterol, it does not have any bearing on whether that person will get asthma in the first place.

The genetic variant is predicting individual physiological responses to drug molecules, not the biochemical processes that caused the

disease being treated. And when SNP patterns are analyzed together, as a sort of DNA bar code, they will predict drug responses without revealing anything about the actual genes on which the SNP's occur.

Bartha Maria Knoppers, a law professor at the University of Montreal, who is chairwoman of the international ethics committee of the Human Genome Organization, an international organization of scientists who are working on finding the sequence of the human genome, said she thinks that the benefits of the new approach are overwhelming.

"People will probably look with some suspicion on claims that this will ultimately be beneficial because it is in our cultural milieu to say 'Oh, another marketing ploy,'" Ms. Knoppers said.

But "I think that, provided we proceed with caution, that it can be very beneficial," she added. "There are drugs that don't work for many people, there are drugs that are dangerous. I would think that making drugs more therapeutic and safer surely is an ethical goal."

Next in Business Day: Makers of chips used in DNA analysis are rushing to capitalize on the move toward tailor-made drugs.

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