Testing Genes

Physicians wrestle with the information that genetic tests provide

By LISA SEACHRIST

A carrier of the gene for hemophilia, Queen Victoria of England inadvertently spread the disease to many royal families of Europe. Alexandra, the wife of Tsar Nicholas II of Russia, was Victoria's granddaughter and a carrier. Unraveling the inheritance pattern for hemophilia was easier than today's challenge of understanding the genetic components of many complex diseases.

Over the past decade, scientists have unearthed a dizzying number of genes responsible for human ailments. Now, as widespread genetic testing is poised to become a reality, many physicians find themselves conveying information that they don't fully understand. "Docs know what it means to order [blood tests]," says Michael S. Watson of Washington University School of Medicine in St. Louis. "But many don't understand the type and limitations of information that a genetic test delivers."

In fact, Watson notes, medical genetics became a recognized specialty only 14 years ago, and only 800 physicians are certified in the field. As recently as 1987, only 50 percent of U.S. medical schools trained students in human genetics.

Physicians, even those highly respected in their specialties, are not prepared to deal with all the possible results and implications of the genetics.

Consider the experience of cardiologist Daniel J. Rader. He didn't think twice about ordering a genetic test for his patient. The middle-aged woman had extraordinarily high cholesterol that he thought might stem from a genetic disorder known as type 3 hypercholesterolemia. If it did, Rader knew he could lower the concentration of cholesterol in her blood with medications.

He sent a vial of the woman's blood to a laboratory at the University of Pennsylvania in Philadelphia, where colleagues would determine which types of apolipoprotein E (apo E) DNA the patient carried. Apo E, a protein that transports cholesterol, comes in three varieties—E-II, E-III, and E-IV. Everyone inherits two copies of the genetic information needed to produce apo E, one from each parent; each copy codes for one of the three apo E varieties.

Rader suspected that his patient was one of a relatively small number of people possessing two copies of the apo E-II gene, which would account for her astonishingly high cholesterol.

The test revealed a much more complicated picture. The women had inherited two copies of the gene for apo E-IV, not apo E-II. Several studies indicate that presence of two copies of apo E-IV increases a person's risk of heart disease by 30 to 50 percent. While Rader was informing his patient of these implications, she happened to mention that her memory had begun failing.

Suddenly, all bets were off. Rader knew that some neuroscientists maintain that inheriting two copies of apo E-IV virtually guarantees developing Alzheimer's disease by the age of 80 (SN: 1/1/94, p.8; 5/7/94, p.295), although the ability to predict Alzheimer's is by no means certain.

Rader's patient had already begun to display the earliest signs of dementia. "This patient had symptoms, so I had to tell her about the possibility that she could have Alzheimer's," Rader said in an interview.

By all accounts, his patient took the news well. Nonetheless, Rader balks at the prospect of having to counsel more patients about a disease far outside his expertise as director of Penn's lipid clinic. "To be perfectly honest, I am [now] much less likely to order this test."

As genetic tests proliferate, more and more physicians can expect to face Rader's dilemma: how to help patients understand the results of genetic tests that they themselves are ill-prepared to interpret. In addition to the information such tests yield, the testing industry has sprouted up so quickly that its practices remain largely unregulated.

At the annual meeting of the American Society for Human Genetics in Minneapolis this October, scientists presented data questioning the ability of physicians to interpret genetic information and counsel patients. They also challenged the standards and accuracy of the laboratories conducting genetic tests.

Human genetics began with the study of rare diseases that obey the rules of inheritance described over 100 years ago by Austrian monk Gregor Mendel. Huntington's disease, for example, arises from a dominant genetic flaw: People with one bad copy of the relevant gene get Huntington's disease. Other conditions, such as Tay-Sachs disease and sickle-cell anemia, follow the rules of recessive inheritance: Only people who inherit a flawed copy of the gene from both parents will get the disease. A person who inherits one flawed copy of such a gene remains healthy but can pass the mutant gene on to his or her children.

Early doctors noted that even these Mendelian genetic patterns could be difficult to interpret. For example, hemophilia afflicts men in much greater numbers than women. Scientists went on to discover that the gene for hemophilia lies on the X chromosome. For women, the gene more or less follows recessive inheritance patterns, but for men, who have only one X chromosome, inheriting one copy of a flawed gene results in disease.

Unfortunately, most diseases don't follow the rules set forth by Mendel. With the advent of powerful molecular techniques, researchers began to uncover genes that predispose people to health problems rather than directly causing disease. Recent discoveries include genes that predispose people to diabetes, certain cancers, and cardiovascular disease. Scientists have even unearthed a couple of genes associated with the never-ending

battle of the bulge. Such conditions are probably attributable to several genes in combination with an individual's lifestyle. Thus, quantifying a person's risk of these diseases is extraordinarily difficult.

Even more difficult is determining whether a gene that causes a disease in high-risk families causes the disease in the population at large. For example, in high-risk families, inheriting a mutation in the *BRCA1* gene gives a woman an 85 percent chance of developing breast cancer. Scientists have identified 65 different mutations on this large gene so far, any one of which may pose some risk of breast cancer (SN: 9/24/94, p.197). Physicians ordering a genetic test must not only look for all of these possible mutations, but also determine the risk each mutation holds for the individual.

To make matters even more complicated, it is possible that mutations in other genes besides *BRCA1* appear with unusual frequency in high-risk families and may influence a person's breast cancer risk. For all these reasons, geneticists usually warn against expecting a widespread genetic screening test after studies in high-risk families link a new gene to a disease.

Even where a genetic test is available, many physicians are not able to inform patients accurately of the pros and cons of testing, including the limitations of tests, or identify situations in which testing is appropriate.

Telling patients about the limitations of a genetic test can drastically alter their desire for testing. A survey of women undergoing routine mammography revealed that 90 percent of participants would want to be tested for *BRCA1*. Neil A. Holtzman and Gail Geller at the Johns Hopkins Medical Institutions in Baltimore questioned this reported interest. In a subsequent study, they found that the number plummeted when women learned that most breast cancer is not associated with inheriting a mutant *BRCA1*, that doctors can offer no way to prevent breast cancer, and that disclosing positive test results to health insurers could result in loss of health insurance (SN: 1/21/89, p.40).

"Any evidence of substantial interest in genetic susceptibility testing in the absence of efforts to educate [people] about the limitations as well as the benefits should be interpreted very cautiously," Geller and Holtzman note in the December NATURE GENETICS.

Physicians may lack the expertise to identify situations in which testing would probably benefit the patient. Colette G. Fakoya of the Medical College of Ohio in Toledo surveyed 120 family practitioners and pediatricians in northwest Ohio to find out how often they referred patients with suspected genetic diseases for genetic evaluation. Fewer than half referred patients they suspected had neurofibromatosis or fragile X syndrome—one of the commonest causes of mental retardation—for further evaluation. Many said that there was nothing that could be done for these patients, so genetic evaluations served no purpose.

Fragile X patients, however, often suffer from mitral valve prolapse, and they need antibiotics when visiting the dentist. Moreover, the mother of a fragile X child could be advised about the risk of having another affected child (SN: 6/8/91, p.359). In the case of neurofibromatosis, which carries an increased risk of brain tumors and certain cancers, diagnosis could allow physicians to care for their patients more effectively (SN: 7/28/90, p.61; 8/18/90, p.101).

The most telling aspect of the survey, Fakoya notes, is that over 90 percent of responding physicians feel inadequately prepared to use genetic testing and give diagnoses.

The practices of laboratories that provide genetic testing give many geneticists pause. Holtzman and his colleagues studied 463 commercial and nonprofit laboratories that are developing or offering genetic tests and found that nearly 90 percent are registered under the Clinical Laboratories Improvement Act of 1988 (CLIA), which sets standards for medical tests.

Nevertheless, 41 percent of commercial laboratories are using testing methods without the oversight required by the U.S. Food and Drug Administration, and 26 percent of the nonprofit groups do so without institutional review board oversight. Close to 30 percent of both commercial and noncommercial labs use home brews—reagents prepared in-house that have never been validated by an outside source. According to Holtzman, at least one researcher said that he considered publication in journals validation enough.

Holtzman is quick to point out that both commercial and nonprofit laboratories are concerned about maintaining the highest levels of accuracy and legitimacy in their tests. He further notes that FDA could modify its regulations to address the idiosyncrasies of genetic testing. Currently, "CLIA is not requiring proficiency tests for genetic labs, even though such programs exist," he says.

In addition to questionable quality control, the Johns Hopkins team discovered some disturbing trends in how the laboratories administer their tests. Twenty-seven labs said they test for Alzheimer's disease, breast cancer, or hereditary nonpolyposis colorectal cancer. Those tests are considered purely investigational by the American Society for Human Genetics and the American College of Medical Genetics. Thirty-seven percent of the companies and 75 percent of the nonprofit organizations market their tests to nongeneticist physicians, even though only 20 percent of the companies and 6 percent of the nonprofit labs think most physicians can interpret the results adequately.

Dorothy C. Wertz and her colleagues at the Shriver Center for Mental Retardation in Waltham, Mass., found that nearly half of the 186 laboratories listed with Helix, a registry of U.S. laboratories performing genetic tests, will test patients directly—without a referral from a doctor or counseling about the implications of the test. Wertz says she "was appalled that tests were so available to the public in general."

More surprising, 62 percent of the laboratories said they would test, at the request of the parents, a 7-year-old to see if the child is a carrier of the cystic fibrosis gene. "Genetic tests should have a benefit to the child being tested," says Wertz. "With the exception of presymptomatic testing for familial polyposis coli [a genetic disorder resulting in colon cancer], there is no documented benefit to the child of testing for cystic fibrosis carrier status or presymptomatic testing for Huntington's disease."

Faced with a burgeoning and largely unregulated genetic testing industry, a joint working group of the National Institutes of Health and the Department of Energy formed a task force on genetic testing in early 1995. Holtzman and Watson serve on the task force, which is examining the strengths and weaknesses of current genetic testing policies and practices with an eye to making recommendations on how the government should regulate genetic testing.

To date, the group has established the principles that each new test must have performance specifications, new tests should be externally validated, and laboratories should be required to meet proficiency testing standards. The task force also plans to address the need for proper counseling about carrier status and for educating nongeneticist health care providers. The group aims to issue specific recommendations in 2 years.

In the meantime, the dilemmas involving genetic testing will probably worsen. Women with relatives recently diagnosed with breast cancer will likely demand *BRCA1* testing. People will probably flood doctors' offices with demands for colon cancer tests (SN: 3/19/94, p.182) and Alzheimer's tests. Yet, the age of widespread predictive screening for these disorders remains in the future.

As Watson points out, people can handle the bad news associated with inheriting genes that predispose them to disease. "But the second you tell a patient, 'Your risk is increased,' they say, 'How much?' If you don't have that answer for them, you haven't done them much good." □