

# The Challenges of *Personalized*

**FOR PERSONALIZED MEDICINE TO BE REALIZED, “WE HAVE TO COLLECT ENORMOUS AMOUNTS OF INFORMATION. AT THE PRESENT TIME, WE ARE BETTER AT COLLECTING THE INFORMATION THAN TRULY UNDERSTANDING IT.”**

**W**hat is the reality of personalized medicine? It turns out that it depends on whom one asks.

“It is not a particularly straightforward issue,” explained Garrett FitzGerald, M.D., director of Penn’s Institute for Translational Medicine and Therapeutics and chair of the Department of Pharmacology. He was speaking at a recent symposium presented by the Penn Genome Frontiers Institute (PGFI) and the Franklin Institute, the venerable Philadelphia institution dedicated to public science and technology education.

“Open Society and Genomics-Enabled Personalized Medicine” was moderated by Gina Kolata, science writer for *The New York Times*. The session included talks by leading researchers and bioethicists.

The promise of personalized medicine became clearer in 2001 when the International Human Genome Project completed a blueprint of the human genome. Researchers began to realize the possibilities based upon the new knowledge that could enable novel approaches toward managing and curing human disease. It was as if a new era in medicine was being born.

Not so fast: that seemed to be the consensus of the speakers at the symposium. Although they acknowledged the great promise of personalized medicine as en-

abled by genomics – the study of how an organism’s complete genome is regulated – there are still some obstacles and some significant questions to address. As FitzGerald put it, “The challenges of personalization are medical and technical, social and political, economic and regulatory.”

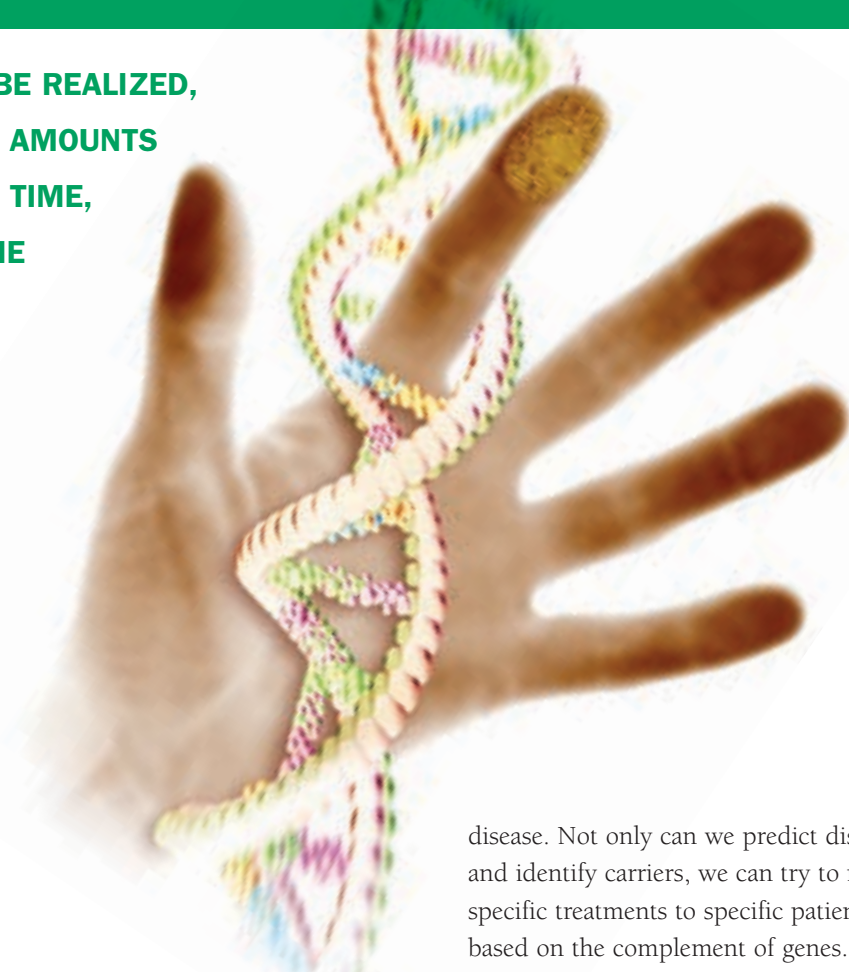
Tom Curran, Ph.D., a professor of pathology and laboratory medicine at Penn who serves as an associate director of PGFI, began the symposium by discussing some of the successes of gene therapy.

“As human beings, we have a lot in common,” he said. “Our DNA differs in only 10 million base pairs out of three billion, so we are actually 99.7 percent identical.”

By interpreting the information contained in DNA, he continued, “we can learn about nature and the origins of

disease. Not only can we predict disease and identify carriers, we can try to match specific treatments to specific patients based on the complement of genes. We can also uncover the causes of diseases and hopefully can offer new treatments to our patients.”

Curran, who is also the deputy scientific director of The Childrens Hospital of Philadelphia, described how investigators are using genomics to try to understand cancer. Recently, scientists at CHOP discovered a mutation in a single gene that exists in about 25 percent of patients with neuroblastoma, a neuroendocrine tumor that is the most common extracranial solid cancer in childhood. “It turns out that this mutation was not a new discovery,” said Curran. “It had previously been found in patients with adult leukemia. To treat these adult patients, a drug was developed. Now, one year later, we are beginning clinical trials to learn if this drug is also effective against neuroblastoma.”



Getty Images/Steven Hunt

# Medicine

By Nan Myers

Scientists are also using gene therapy to “cure” sickle cell disease, he said. “Sickle cell is a terrible disease that causes great pain. It is a genetic disorder that forms a mutation in hemoglobin. It binds oxygen in a slightly different way than normal to form a cell in the patient’s blood that looks like a sickle rather than being round.”

“There is a cure for sickle cell disease,” Curran asserted. “It is bone marrow transplant. If there were a perfect match for every patient, we would cure the disease. Since we can’t, scientists at CHOP are pioneering a new approach to transplantation, called tolerance.” In this process, they transplant the mother’s blood, which does not have the disorder, directly into the fetus *in utero*, before the immune system in the fetus is developed. “The hope is that we can trick the fetus into believing that the mom’s blood is the baby’s blood – and have a baby born without sickle cell disease.”

Each speaker at the symposium emphasized that the study of genomics and personalized medicine is extremely expensive and takes both significant amounts of time and very specialized research. “There is a lot being promised,” noted Pamela Sankar, Ph.D., assistant professor of bioethics in Penn’s Center for Bioethics. And as Curran pointed out, “We have to collect enormous amounts of information. At the present time, we are better at collecting the information than truly understanding it.”

The mission, according to FitzGerald, is to learn “how the revolution in genomics may refine the way we use the drugs we have today and help us to refine the use of drugs that are discovered tomorrow.” He went on to explain an addi-

tional complication in the coming era of personalized medicine.

“Most of us are subject to the determination of two professions, medicine and law,” which, he said, think differently about the same type of evidence. “Medicine uses large-scale clinical trials in a large number of people to determine if drugs work safely or if they work at all. Law looks at things in a much more personal fashion; it is much more interested in knowing whether the drug caused *your* heart attack or *your* stroke. In a sense, the law is already at the personalized stage of medicine.”

In the current health-care environment, FitzGerald continued, “Drugs are effective; they are also dangerous. Take Celebrex,

## **THE HUMAN GENOME IS IMPORTANT, OF COURSE. “BUT HOW DO THESE MULTIPLE CLUSTERS OF MULTIPLE GENES INTERACT WITH THE ENVIRONMENT THAT ONE IS EXPOSED TO – WITH DIET, EXERCISE, AND SMOKING, FOR EXAMPLE?”**

for example. Packages carry an FDA-mandated ‘black box warning’ for cardiovascular and gastrointestinal risk. Yet we know this risk only pertains to two percent of the people. But how do we know which people are in that two percent?”

Sankar elaborated on this challenge. “The future of personalized medicine is pharmacogenetics,” she said. “This is the concept of choosing a drug just based on a person’s genetics. The hope is that in the future they will do a genetic analysis of you and on the basis of the results, get sufficient information to decide if you should get a specific medicine and how that medicine should be dosed or whether, instead, there are certain preventive measures you are recommended to take.”

On the other hand, the challenges of personalized medicine have not slowed the movement. “The market has already

spoken,” said FitzGerald. “There are people out there who are ready to sell information to you on your personal genome. Look at those companies who offer genome mapping services, who offer to let you see your genes in a whole new light. Spend, swab, send – within days, you can unlock your susceptibility to certain diseases and so much more.”

According to Sankar, “People have an incredible optimism for personalized medicine.” But, she argued, the reality today is very different. It is a very complicated process, both creating a test and getting the test to the point where it can actually be used in a clinical setting. Sankar also raised concerns about interpreting test results, citing a recent study that looked at a colon cancer test and how well the physicians could use the information. The study showed that more than 30 percent of the physicians could not interpret the results correctly. “So the question is: If the physician who sees the test results can’t really explain them to a patient, what is the likelihood that a patient can understand the choices?”

How significant are genomes in determining a person’s health? FitzGerald suggested that they are only one factor, and the panel concurred. “We’ve taken our eye off the total problem to focus on only part of the problem,” said FitzGerald. Instead, humans can never really get away from “the environmental influence. All of the aberrant genes we find can contribute to what we know as a heart attack or stroke. But how do these multiple clusters of multiple genes interact with the environment that one is exposed to – with diet, exercise, and smoking, for example?”

These are the kinds of questions that will have to be answered before the promise of personalized medicine can become a reality. ▀

Materials related to the symposium can be accessed at <http://published.genomics.upenn.edu/2009/franklin>