NEW BIOLOGY & PUBLIC POLICY SEMINARS

A SERIES COSPONSORED BY CSIS AND THE WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH

April 2001

The Interface of Biomedical Research and Public Policy in the Genomic Revolution

Lightning advances in deciphering the human genetic code are propelling our society into uncharted waters and raising profound issues at the juncture of science and policy-issues that must be addressed soon, according to speakers at a seminar sponsored by the Center for Strategic and International Studies (CSIS) and the Whitehead Institute for Biomedical Research. Illustrating this point, scientists posed questions that go to the heart of the social contract between citizens and their government, from privacy rights to public trust. This issue brief presents highlights of the New Biology: Challenges and Opportunities, the first in a series of briefings convened in Washington, D.C.,on March 29, 2001 to stimulate dialogue between leaders in science, medicine, law, and biotechnology and senior government policymakers on matters that will shape much of the genomic revolution's impact on individuals and institutions in this country for the next 10-15 years.

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From Mendel's Laws to Modern Lawmakers

"We are living through the most remarkable revolution in scientific history," according to Dr. Eric Lander, director of the Whitehead Institute's Center for Genome Research. Although people have noticed resemblances between parents and offspring throughout human history, our understanding of an informational basis to life remained vague until 1865, when Gregor Mendel reported the results of his breeding experiments with pea plants. Those landmark findings languished for 35 years. The twentieth century began with publication of three papers on Mendel's laws of heredity and closed with a rough draft of the human genome. "It's not a bad story for a century," Lander said.

A sea change in biomedical research took place around 1980, when genetic knowledge made possible a systematic approach to disease. For diseases known to transmit in families, for example, scientists "examined random bits of DNA up and down the chromosomes" until they found one whose inheritance pattern correlated with the disease. (See Genetics Glossary.) "It became possible to find where causes are without knowing what the causes are," Lander said. From that point, scientists could move along the chromosome from nearby markers to isolate the gene itself. This laborious process, which took five years and hundreds of people at a cost of $50 million, was used to isolate the gene for cystic fibrosis in 1989. Today a scientist can type the sequence for a protein into a computer and have the machine identify similar proteins and their functions, shaving five years off a genetic research project. More than 1,000 diseases have been mapped to chromosomal regions this way.

"You and the person sitting next to you are 99.9% identical at the genetic level," said Lander.

"It was tedious to do this for every disease, and so was born one of the first great infrastructure-building programs in biology," according to Lander. The National Human Genome Research Institute and the U.S. Department of Energy launched the Human Genome Project in 1990 as a 15-year effort to find and sequence all the genes in the human body. Thanks to rapid technological advances, that work will be completed in 2003, two years ahead of schedule. When the human genome sequence is complete, it will be like a parts list-a finite number of building blocks, in this case, some 30,000 genes. Lander explained the value of having such a list of all the variations. "The amount of variation between any two people in this room is only about 1 letter in 1,300. You and the person sitting next to you are 99.99 percent identical at the genetic level," he said.

To illustrate the potential importance of this small degree of variation to individuals and to research, he used apolipoprotein E (apoE) on chromosome 19. ApoE has its own variants of E2, E3, and E4. Any person who is homozygous for E4-that is, has a double dose of it genetically-has a 60-70 percent lifetime risk of developing Alzheimer's disease. With DNA amplification technology, that genetic information can be gleaned easily from a drop of saliva. Pinpointing apoE's link to Alzheimer's disease has directed the pharmaceutical industry to study this protein's activity and develop drugs that may substantially delay the devastating effects of the disease. Lander predicted that variations in the genome will one day be correlated with specific diseases, from asthma to stroke.

At the same time, Lander said that the central challenge of our time may well be how we as a society acknowledge both our fundamental sameness and our genetic differences, while avoiding the pitfalls of genetic determinism. Expressing concern thatpeople will see themselves as limited by their genes, Lander said, "This would be a terrible mistake. There is no genetic evidence whatsoever to support this kind of genetic determinism."

Eric Lander, director of the Whitehead Center for Genome Research

Changing the Basis of Biomedical Research and Treatment

What is the medical promise of the new biology? At a fundamental level, it will help us understand the molecular mechanisms of disease. "It would be immoral not to undertake research that gives us a chance of understanding what the basis of human medical suffering is about," said Lander. "We owe it to our children." The result will be better therapies because we will be able to target treatment to underlying causes of disease rather than symptoms, classify diseases by distinct subtypes that respond to different treatments, and classify side effects.

Preventive therapies are another potential benefit, he said. Some drugs may be developed to slow a process decades before the disease becomes symptomatic, posing an interesting challenge for the pharmaceutical industry: How can a clinical trial be designed to demonstrate a drug's effect on something that has not developed?

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The ultimate result of this knowledge, he commented, will be a much more systematic approach to biomedical and pharmaceutical research that will not only improve treatment but lower the cost of drug development by boosting the industry's success rate, which is now only 1-2 percent.

"How fast we go will be determined by how well organized we are, how much we fund science, and importantly, how we deal with the social issues," noted Lander.

Speculating on a timeline for these advances, Lander said, "I feel confident that we will have largely dealt with cancer by the end of this century. How fast we go will be determined by how well organized we are, how much we fund science, and importantly, how we deal with the social issues."

He raised a critical issue about moving too fast. Some people will be pressing to attempt improvements on the human genome "long before we can do them safely," Lander warned. "And even if we do ever have the base of knowledge to do it responsibly, do we wish to regard human beings as products of manufacture?" he asked. "Tinkering with a system we barely understand-the hubris in that is truly spectacular." Dr. Gerald R. Fink, director of the Whitehead Institute, emphasized the importance of distinguishing the cloning of humans from stem cell research: "They are two very different issues scientifically."

The Balancing Act: Scientific Progress and Social Protections

In just a decade, the Human Genome Project has given scientists the tools to understand all the information encoded in the DNA molecule. These tools have raised a wide range of pressing questions about genetics and public policy, said Dr. Philip R. Reilly, chief executive officer of Interleukin Genetics, Inc.

Doctor/Patient Confidentiality. Consider how the genomic revolution is challenging the inviolate nature of doctor/patient confidentiality. What if a patient is diagnosed with a genetically linked form of colon cancer, and his brother has a 50 percent chance of having inherited that gene. If the patient chooses not to tell his brother, does the doctor have an obligation to share that genetic information with the man's blood relatives, and if so, how does he reconcile that with patient confidentiality?

Phillip Reilly, CEO of Interleukin Genetics

Today there are no rules or guidelines for the sharing of genetic information across families. Over the next 20 years, Reilly expects a move toward a more family-centered notion of confidentiality-"a world in which physicians have the right, but not the obligation, to make limited disclosures to third parties about DNA information."

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Health Insurance Discrimination and Coverage. In the area of health insurance and discrimination, Reilly noted that, with the exception of one section of the Health Insurance Portability and Accountability Act of 1996, "we do not have a federal law that protects genetic information." About 39 states have enacted such laws. Reilly favors broad antidiscrimination laws that apply to all medical information, "to protect against the use of medical information to keep people out of the health insurance system or to charge them much higher rates."

Looking ahead, some day a more reliable genetic test for Alzheimer's disease will be available. "Can insurers demand that you have a test you don't want? Can they demand access to tests you've already had?" Lander queried. The risks of disclosure may deter people from having a test that may be medically beneficial. What if the long-term care insurance industry requires genetic screening and refuses to sell insurance to applicants whose genetic tests show a high risk for the disease, Reilly queried.

Do the new genetics change the very concept of disease, and what is covered under insurance? Consider the case of a Nebraska woman with a strong family history of ovarian cancer who had her ovaries removed prophylactically. When her insurance company refused to approve the procedure, she had it done outside the plan and sued to recover the cost of the surgery. At issue was a single question: Did this woman meet the insurance contract's criteria for "disease or disability"? She was healthy at the time of surgery, and the pathologist found no evidence of disease in the ovaries. By a vote of 4-3, the state Supreme Court held that, under the contract provisions, she qualified for coverage. Clearly, Reilly commented, this is a matter of public policy.

Workplace Issues. In the arena of genetic information and employment, "we are at the very outset of an important public policy debate, and so far, I think it's not gone very well," according to Reilly. A few states have enacted laws that prohibit genetic testing for any reason in the workplace, but that approach does not adequately address the complexity of the issues. For example, he asked, what if some people's genotype put them at very high risk for a disease if they're exposed

to a certain chemical in the workplace, and it's possible to ascertain that risk? "We want to be able to use the information to protect individuals, not to just prohibit the exposure," he said.

Public Trust. Understanding the molecular mechanisms of disease and their variations requires sizeable study populations. Recruiting and funding for such studies, Lander said, is less a scientific or technical problem than a social problem. Finland, for example, has a national health care system, a population that has "extraordinary trust in its government," and very high rates of participation in large population studies. "We will not be able to pull this off without a trusting population, and we're going to have to earn that trust," he said, by developing protections for genetic information.

Issues of both privacy and public trust come into play in genetic research involving human subjects. In the United States, most such research is conducted through institutional review boards, a local system of oversight that is being attacked as overburdened and underfunded, with attendant risks for participating patients. In fact, Reilly pointed out, there are no rules governing human subject research that is conducted without federal funds, and he expects Congress to address this topic in the coming years. Even the existing federal rules were created long before the genetic revolution, when the primary concern was physical harm. In the era of genetics, however, the overriding concern is informational harm-the inadvertent or deliberate sharing of genetic information that can affect employment or insurance.

Another matter of public trust involves genetically modified food. In the United States, "we have been spared the bitter and economically dangerous debate that is occurring in Europe," Reilly said. The public trust in Europe has been lost, Lander added, "because government and scientists together failed to deliver thoughtful, careful, trustworthy analysis." In the early 1990s, the Food and Drug Administration issued a proposal not to disclose on food labels any genetically modified contents. Reilly questioned the wisdom of that policy decision: "Why not, if it's safe, label it?" he asked. "Sure, there's some cost associated with labeling it, but I think there's a greater cost associated with not labeling it if it breeds suspicion."

Patents. Genetic research is rapidly changing patent law. Genes are already patentable by their discoverers, but patent lawyers are exploring technologies that will allow them to file patents on all molecules affecting a particular receptor for a specific disease. "We are now granting, without anybody paying attention to it, patents on all possible molecules, including ones that haven't been invented." This policy will block all "me-too" drugs, derivative products such as different molecules against the same receptor, Lander cautioned. He sees danger in this direction, because historically, such drugs have driven down the cost of pharmaceuticals through competition. "There's clearly a role for private industry," Lander added, "but as a society, we have an obligation over the course of the next 20-30 years to lay a foundation which is not patentable."

Reexamining the Criminal Justice System

From his work with the Justice Department's Commission on the Future of DNA Evidence, Reilly has seen how rapidly genetic information is changing the criminal justice system. In just 10 years, all 50 states have enacted laws for DNA felon data banks that can communicate through a common language. Now, a sample from a crime scene can be run through a very large, national database, making it possible to exonerate the wrongfully accused quickly, focus prosecution on those who were at the crime scene, and aid those who have been wrongfully convicted. In the last three years, 100 people convicted of felonies have been released from prison because their DNA did not match evidence from the victim.

Money is one of the biggest problems plaguing DNA forensics in the United States today, he said. Few states that have enacted the laws have appropriated funds, and the federal government has made "only a small financial gesture toward dealing with the backlog problem-the half a million samples collected pursuant to these laws that have not been analyzed."

The use of DNA to identify possible criminals raises other thorny issues. As an example, authorities in Florida suspected a man for a violent crime, but they did not have adequate probable cause to obtain a blood sample to compare with their forensic DNA evidence. They trailed him, and eventually saw the suspect spit in a parking lot. They collected that sample, analyzed it, found that it matched with evidence, and arrested him. However, Lander pointed out that simply by wiping their mouths with a napkin, people usually leave enough cells for DNA typing. "In Washington, how long will it be before an enterprising reporter does this for a presidential candidate? And what about each member of Congress? Does the public have a right to know your full genotype?" he asked. At present, no laws prevent anyone from collecting napkins and revealing genetic information about any of us.

DNA information is forcing the criminal justice system to reexamine some of its most basic rules, according to Reilly.

DNA information is forcing the criminal justice system to reexamine some of its most basic rules, according to Reilly. One example is the statute of limitations. Some states have a seven-year limit for bringing to trial a person accused of rape. With DNA evidence, however, it is now possible to "identify who an individual must be without knowing his name" and to prosecute him years later. In Wisconsin, a prosecuting attorney has filed a case against John Doe and defined him by his DNA. "Is that a good thing or a bad thing?" he asked. "Do we want to revamp the statute of limitations?" A related legal issue is the principle of finality-that when a case has been appealed and decided, it's over. DNA evidence showing that innocent people have been convicted of felonies suspends that basic legal tenet.

Another basic tenet of the legal system is the presumption that children born within a marriage are the offspring of the husband and wife. Population genetic studies show, however, that 2-5 percent of "presumed paternal biological relationships are not, in fact, true." Men have already filed actions claiming they should not have to pay support for a child raised as theirs but proven by DNA technology to be unrelated. In theory, he said, more than 100,000 children per year could be denied child support on these grounds, raising other issues for our society.

"Should there be a universal DNA data bank covering everyone from birth?" Reilly asked. (This topic will be addressed at the next CSIS/Whitehead breakfast seminar, DNA Forensics: Should the United States Establish a Forensics Data Bank? on May 2, 2001.) The United States already has the makings of a universal DNA bank, he noted. Since 1962, most children born here have had blood drawn at birth for genetic tests; many states have kept the dried blood samples, which are a rich source of DNA. The DNA data banks are proliferating, and there is a paucity of rules to guide them.

Given the range of social and legal issues raised by the genomic revolution, "a challenge to policymakers and members of Congress is to make sure that genetics brings us together rather than separates us," said Reilly.

Genetics Glossary

DNA (Deoxyribonucleic acid): The genetic material of living organisms; the substance of heredity. It is a large, double-stranded, helical molecule that contains genetic instructions for growth, development, and replication. The rungs of this double helix are made of base pairs.

Base pairs: Pairs of complementary nitrogenous bases that interact to form each rung of DNA's double helix. Adenine (A) pairs with thymine (T); cytosine (C) pairs with guanine (G).

DNA sequence: The order of four nucleotide bases along each DNA molecule: adenine (A), thymine (T), cytosine (C), and guanine (G).

Genes: Specific sequences of nucleotide base pairs that function as the fundamental units of heredity.

Human genome: The "master blueprint" of approximately 30,000 genes that provide the instructions to make a human being and tell the cells in the body what to do.

This issue brief was written by The Stein Group.

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Funding for this series has been provided to CSIS and the Whitehead Institute from The W.M. Keck Foundation, The Richard Loundsbery Foundation, and the U.S. Department of Energy Office of Biological and Environmental Research.