

QnAs with Eric S. Lander

This year marks the 10th anniversary of the sequencing of the human genome. More than two decades after the launch of the Human Genome Project, researchers have made remarkable inroads into unraveling human biology, evolution, and disease. As the tools of genome sequencing and analysis grow more sophisticated, insights into the human genome will slowly shift the terrain in the treatment of disease. To be sure, the shift has already begun. Eric Lander, founding director of the Broad Institute of Harvard and Massachusetts Institute of Technology and a member of the National Academy of Sciences, offers PNAS readers his perspectives on the role of genome sequencing in the transformation of medicine.

PNAS: The cost of genome sequencing has plummeted since the start of the Human Genome Project. In 1990, sequencing a single genome cost an estimated 3 billion dollars. Now, researchers envision \$1,000 genomes within the next five years. What has led to the drop in cost?

Lander: Two factors have contributed to lowering the cost of genome sequencing. The first is what can be called economic pump priming. Back in the 1950s, the Department of Defense signaled to industry that it would be a major customer for semiconductor; this jumpstarted the market, calling forth private investment that improved technology and drove down prices. In the 1990s, the Human Genome Project had a similar effect; the federal government signaled to industry and academia alike that DNA sequencing would be really important. New creative ideas for genome sequencing were called forth, and the cost dropped substantially. The second factor is a technology shift that has occurred in the past 5 y from capillary electrophoresis of hundreds of samples to optical detection of billions of samples on a slide. Altogether, costs have fallen by more than 1 million-fold since the start of the Human Genome Project. That has led, in turn, to the generation of stunning amounts of information and the creation of a thriving field of computational biology.

PNAS: How can genome sequence information help physicians test for and treat common genetic diseases, which are typically tied to many genetic factors?

Lander: We want to understand the genetic basis of all major human diseases, including inherited factors in diabetes, Alzheimer's, autoimmune diseases, schizophrenia, and bipolar disorder and somatic mutations in every type of cancer. It's important to understand that there are two different goals in studying genes involved in common diseases. The pri-



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mary goal is to understand the biological pathways underlying disease, because that's what's fundamental to treating disease; there's already been remarkable progress toward this goal. A secondary goal is to be able to provide individual risk prediction for disease; this goal is maybe only partially feasible and is, in my opinion, less important.

Understanding the disease-related cellular pathways forms the basis for many drug development efforts in the pharmaceutical industry. This knowledge often turns out to be useful even in individuals without the particular genetic variants that were used to identify the pathways. A good example is familial hypercholesterolemia caused by mutations in the LDL receptor that lead to high levels of LDL cholesterol and heart disease. Although familial hypercholesterolemia is relatively rare, the genetic understanding of the condition led to the development of cholesterol-lowering drugs, or statins, which are taken by tens of millions of people who don't carry an LDL mutation.

PNAS: To unravel the genetic basis of common diseases, you have noted that we might need to sequence a million genomes. Can you explain the idea?

Lander: To have adequate statistical power to identify the genes in which rare genetic variants increase risk for a disease by twofold, you can calculate that you'll need to sequence more than 5,000 cases and 5,000 controls or about 10,000 genome samples. When you multiply this by more than 100 diseases, you realize that we'll end up needing information from more than 1 million genomes. As the

cost of genome sequencing drops to \$1,000, the cost for each disease would be about \$10 million. When you think about how much money is spent on schizophrenia or other diseases, doesn't it make sense to invest to find all of the human genetic information that is potentially relevant to the disease?

PNAS: Translating the understanding gained through genome analysis into tests and treatments for people is a painfully slow process. Can you explain why a revolution in medicine requires decades of research?

Lander: Genomic research has already led to major clinical advances—notably in cancer. However, realizing the full benefits will take much longer. People who understand the process of scientific progress in biomedicine know that you can't go from a draft sequence of the human genome to revolutionary cures for diseases in 10 y. There's a lot of work to do along the way: finishing the genome sequence, understanding the contents of the genome, identifying genes involved in disease, understanding the underlying biological pathways in which they function, developing drugs against targets, testing the drugs, and then getting drugs approved. It takes at least 30 y for a scientific revolution to have a major impact in medicine. It took more than 50 y to go from the germ theory of disease to the widespread availability of antibiotics or from the idea that cholesterol might play a causal role in heart disease to the widespread use of lipid-lowering drugs. I think we can do better, but we should be clear with the public that truly transforming medicine is not an overnight affair.

PNAS: The Human Genome Project paved the way for synthetic biology, which aims to assemble custom-designed cellular circuitry for reengineering cells for novel functions. How can synthetic biology transform medicine?

Lander: The ability to write new genetic circuits could end up proving tremendously valuable in the future. We're still amateurs at synthetic biology; no one has really written bold new circuits that instruct cells to do important things that they couldn't do before. However, there's a new generation of young scientists coming along with a gleam in their eyes about the promise of synthetic biology. They might want to write circuits, for example, that could allow cells to carry out surveillance for cancer and autoimmunity. Ultimately—and we're talking decades from now—synthetic biology will prove to be a powerful way to program biology. Small-molecule therapeutics can do that in some cases, but synthetic biology may greatly expand the repertoire.

Prashant Nair, *Science Writer*