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When Will Genomics Cure Cancer?

A CONVERSATION WITH THE BIOGENETICIST ERIC S. LANDER ABOUT HOW GENETIC ADVANCES ARE TRANSFORMING MEDICAL TREATMENT

By James Fallows

Since the beginning *of this century, the most rapidly advancing field in the life sciences, and perhaps in human inquiry of any sort, has been genomics. In 2001, rival teams from the Human Genome Project and the private company Celera each announced a draft sequence of the human genome—a map, essentially, of the 3 billion letters of DNA that make up a human being's genetic code. Eric S. Lander was one of the leaders of the public project. Now a professor at MIT and Harvard Medical School as well as the director of the Broad Institute in Cambridge, he discusses what researchers have learned since then, and how they may soon convert many forms of cancer from fatal afflictions to manageable chronic diseases.*

James Fallows: Everyone has heard about remarkable breakthroughs in genomics, but it is hard for nonscientists to put them in perspective. By analogy to aerospace, are we still at a stage like the Wright brothers'? Or are we landing on the moon?

Eric S. Lander: A good analogy is the germ theory of disease. There was a sweep of progress from the fundamental understanding around 1870 that microbes caused infectious diseases, to the widespread availability after World War II of cheap penicillin that saved millions of lives. That took about 75 years. With genomics, we're maybe halfway through that cycle—something like the situation around 1915, when early, highly imperfect antibiotics were first introduced.

JF: What are the comparable next steps in genomics?

ESL: Before we could understand the genetic basis of inherited diseases and cancer, we first had to get a sequence of the human genome. The first 15 years of work [on the Human Genome Project], and about $3 billion of cost, was devoted to getting one sequence of one human being, to use as a starting reference point.

The next job was to go figure out how people with a disease, whether it's diabetes, schizophrenia, or a lung tumor, differ from that reference. That would require looking at the genomes of thousands and thousands of people to spot the changes. Remember that it took 15 years and $3 billion just to get the first person's sequence. The idea of doing that thousands of times over would have seemed crazy—except that an amazing transformation over the past 12 years brought down the cost of sequencing genomes by about a million-fold. That has allowed us to look at thousands of people and see the differences among them, to discover critical genes that cause cancer, autism, heart disease, or schizophrenia.

For the first time, after 25 years of genomics, we can finally pop the hood on the car and see what's wrong. The rate of progress is just stunning. As costs continue to come down, we are entering a period where we are going to be able to get the complete catalogue of disease genes. I think in another five or six years, we should have a complete catalogue. That is not a *cure* for disease. The next level will be seeing how these individual genetic components fit together, into circuits. You could say that right now we are discovering all the parts of a Boeing 747 and meticulously laying them out on the floor of a hangar. That's actually pretty impressive, to get all the parts! Still, the plane doesn't fly yet. This next generation of young scientists is figuring out the functional circuits into which all these parts fit.

JF: I feel lowbrow asking this, but on what timeline will patients see the results? Are these therapies decades away, or a few years?

ESL: It's important to define your goals. Therapeutic development has already been transformed by genomics. There are 800 different anticancer drugs in clinical development today. Cancer drugs used to be just cellular poisons, but almost all of these new ones are targeted at particular gene products that have been discovered.

But it's just a start. Some of the new cancer drugs can miraculously make tumors disappear. The problem is that, a year later, the cancer in many cases comes roaring back, because some of the cells have developed mutations that make them resistant. So genome scientists are now finding and targeting these mutations as well. Remember in the 1980s, when HIV was a fatal disease? What made it become a chronic, treatable disease? It was a combination of three drugs. Any one of those drugs alone, the virus could mutate its way around. But with the combination of all three, the chance that a virus could find its way around all of them was vanishingly small.

That's what's going to be happening in cancer. If you didn't know the HIV story, you would be depressed: you put all this work into the drug, and a year later the cancer has developed resistance. But if you understand that this is a game of probability, and there is only a finite number of cancer cells and each has only a certain chance of mutating, and if we can put together two or three independent attacks on the cancer cell, we win. If we invest vigorously in this and we attract the best young people into this field, we get it done in a generation. If we don't, it takes two generations. That's a very big difference.

JF: You mentioned schizophrenia alongside cancer. What is the genomic prospect for dealing with psychiatric diseases?

ESL: These diseases are the flip side of cancer. Cancer, you can study in a petri dish, because it's about cells growing. You can also inject cancer cells into a mouse and study them. With psychiatric disease, you can't do any of that. It is quintessentially a human condition.

That's why genomics, in which Big Data meets DNA, has been so important for approaching psychiatric disease. By looking at tens of thousands of patients, we've gone from knowing about zero genes underlying schizophrenia, as recently as five years ago, to knowing roughly 100 genes today. And the genes are beginning to make sense. Some look like they're telling us about particular kinds of calcium channels, others about particular ways that neurons grow.

I think the genetic clues as to what's actually wrong in human disease, together with experimental tools of manipulating neurons in animal models, may allow us to produce animals that mimic the real molecular biology of human disease. I'm not Pollyanna. This is not around the corner. It's not for next quarter; it's not for next year. We play for the long game. I don't want to overpromise in the short term, but it is incredibly exciting if you take the 25-year view.

JF: Any researcher can find ways to use extra money. But in genomics now, how significant is research funding as a limiting factor on progress toward therapies?

ESL: It is incredibly limiting right now. Young scientists who need to look at 100,000 cancer samples, or do functional tests inhibiting all the genes in the genome, or explore the use of chemicals in ways they never could before—they need an NIH [National Institutes of Health] that is able to place bets. With sequestration, and the NIH budget falling by about 25 percent in real terms over the past decade, the people reviewing grants naturally become more conservative. When there's less money, reviewers don't want to run the risk of wasting money on something that doesn't work.

I've got to tell you, if you aren't prepared to waste money on things that might not work, you can't possibly do things that are transformative. Because for every successful transformative idea, there's five times as many nonsuccessful transformative ideas. Nobody knows how to figure out in advance which ones they're going to be.

We've got an amazing cadre of young people coming into the field, and they have this cognitive dissonance right now. On the one hand they see unbelievable opportunities, and on the other hand, for the first time they see the nation decreasing funding for biomedical research.

In a very objective sense, this is a unique moment to be investing. This is the first decade when we can actually look across diseases in this systematic way. The idea that we're not investing to let a generation of young people try their riskiest, cleverest ideas is a tragedy. Because we've got such an opportunity.