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The Gene Puzzle

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Ten years ago, the human genome was medicine's holy grail. Playing the part of King Arthur's knights were rival teams of biologists racing to sequence all the genetic instructions required to make a human being. And just as the actual Holy Grail was believed to have miraculous healing powers, some promised that the genome would change medicine forever. Biotech companies raced to cash in—Human Genome Sciences, for instance, filed patents on 100,000 genes and, in 1999, saw its stock quadruple. But genomic science didn't deliver fast breakthroughs. Today Human Genome's stock price is down below $3, and its vast patent portfolio looks like overkill, considering that a human has only about 20,000 genes altogether.

Scientists have made plenty of progress over the past decade in generating genomic data. The Human Genome Project, after employing hundreds of scientists for many years at a total cost of $3 billion, produced in 2000 an error-riddled collage of several people's DNA. Since then, scientists have published complete genomes of five people. And this summer, Complete Genomics, a biotech firm in Mountain View, California, plans to announce that it will sequence an individual genome for $5,000. Data, however, is not the same thing as insight. Rather than finding cures for cancer, diabetes, and other intractable diseases, scientists have mainly learned just how staggeringly complicated genomes are.

One of the most promising techniques for making sense of the data is known as genome-wide association. It entails searching among thousands of people for genetic markers—spots along the human genome where individual letters of DNA vary from person to person. Scientists then look for those markers that tend to show up in people who have a certain disease, but are missing from those who don't. Next the scientists find those disease markers in the complete human genome sequence and begin to search for genes nearby that might play a role. These studies, being large, are slow to yield results, but several have been completed in recent months. In May, two research teams simultaneously published massive studies on blood pressure, based on a combined total of 63,569 people. Between the two studies, the scientists identified 13 new genetic markers associated with high blood pressure.

Cancer researchers are also using genome-sequencing technology to pinpoint key mutations known to arise in certain kinds of tumors, and they're hoping to use that knowledge to create new drugs. In many cases of myeloid leukemia, for example, all the cancer cells depend for their survival on the same protein produced by

the same mutant gene. A drug called Gleevec targets that protein, and, as a result, it has proved to be spectacularly effective against myeloid leukemia. The National Institutes of Health has launched a Cancer Genome Atlas, and scientists in other countries have started similar projects as well.

So far, though, they have found no new Gleevecs. Instead, they've revealed a new frontier in the complexity of genomes. As cancer cells evolve, they tend to acquire mutations that make them more likely to mutate in the future, which means they end up with a lot of mutations that could serve as disease markers. Last November, Washington University biologists sequenced the complete genome of a myeloid leukemia cell, compared it with the genome of a skin cell from the same patient, and found 63,277 mutations in the cancer cell that didn't appear in the skin cell. Scientists are now combing for ones that could serve as targets for drugs.

So far, though, genome-wide association studies have not provided quick fixes for cancer or other diseases. In fact, the markers found in such studies are raising more questions than they are answering. One problem is that the studies typically point to a handful of new genetic markers, each of which accounts for only a tiny amount of the risk of getting a particular disease, leaving most of the risk unknown. It's possible that the genome-wide association studies have missed some genes with powerful effects, and that scientists haven't identified these genes yet because only a few people carry the variants that can dramatically boost disease risk. A second possibility is that hundreds—perhaps even thousands—of variants of genes may influence the risk of disease. These variants may all be very common, but any single one may raise your risk of a disease by a tiny amount. Inheriting only a particular combination of many variants would increase your risk of developing a disease dramatically.

Neither possibility bodes well for genomic medicine. If diseases are controlled by powerful but rare variants, scientists will first have to track them all down. If diseases are caused by common variants in unlucky combinations, scientists will have to test each person for variants on hundreds or even thousands of genes. Doctors who want to treat these diseases won't simply be able to fix a single defective gene in every person with a particular disease; they'll have to sort through a jumble of variations to figure out why some people get sick and some don't.

As complicated as our individual human genomes are, a person's health depends on much more. A human body contains about a trillion cells, but it houses somewhere between 10 trillion and 100 trillion microbes, which have a powerful influence on our well-being. Some help us digest nutrients, others help block dangerous pathogens. In 2007, microbiologists launched the Human Microbiome Project to sequence the genes of these beasts. While each microbe species may have just a few hundred or a thousand genes, collectively they outnumber human genes by 100 to 1. Scientists are compiling a growing catalog of foreign genes, but the data so far do not explain much. Each person's microbial jungle may be a unique mix of species, making it hard to draw any general lesson.

Research on microbes is leading scientists to think about networks of genes that interact with each other in a complex, personal ecosystem. Biologists are using a similar approach to understand how thousands of genes can work together in a single cell. They're adapting the methods of engineering, breaking these gene networks down into components that plug together, much like the components of a radio. If they can do that, they'll have taken a big step toward being able to repair our gene networks when they break down. Don't go betting your stock portfolio that all this will happen next year, or even next decade. But it's a sound wager in the long run.

Zimmer is the author of "Microcosm: E. coli and the New Science of Life.", which will be published in paperback in July.