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I always wanted to be somebody, but now I realize I should have been more specific. —Lily Tomlin



JOSHUA FRANZOS

We can expect that in the next few years it will be possible to map your genome (all of the genes in your cells) for $1,000 or less, thanks to next-generation rapid DNA sequencing technology. Abnormalities in the genome would be seen, as well. With older technology, it would have cost on the order of a million dollars. As you can imagine, there's quite a buzz about this technology, which offers the possibility of identifying the risk of any given disease in an individual, as well as tailoring treatment of diseases to individual patients. But how much will it contribute to making you healthier—to the "personalized medicine" that we hear so much about? Is the technology really going to tell us with precision that any given mutation or polymorphism (the "genotype") means a given disease or disorder (the "phenotype") with certainty? Do our genes always hold our fate?

A report last year in *Science* by Robin Dowell (while at MIT) and others addresses the genotype-to-phenotype problem and is instructive: They saw that two nearly identical genomes managed to bring about two dramatically different phenotypes. The authors used two strains of budding yeast to assess the mechanisms leading to two different results for the same mutation. It became apparent that while the two genomes were indeed nearly identical, the two yeast strains had two different genetic "backgrounds." In this case, background refers to either rare polymorphisms (differences in expression of the same gene), complex combinations of genetic variation, or heritable effects like biochemical modifications (e.g., methylation) to DNA that don't involve actual changes to the molecular-building blocks (nucleotides) in the DNA. Dowell and her colleagues found that a complex set of background-specific modifiers influenced the mutation greatly.

This yeast model likely is very relevant to human disease, given that our most critical genes—those required for viability—are highly conserved in evolution, and they are present in yeast. ("Nature never throws away anything useful.") Moreover, the two yeast genomes are about as similar to each other as the genomes of any two humans.

How much biologically relevant information about us is encoded in our genomes? The genotype-to-phenotype question is a hot issue at the moment as we seek genetic patterns in the malignant cells of individual cancer patients that might tell us which specific drugs would kill the cells and which would not. This strategy, if successful, would revolutionize cancer treatment (and the prevention, diagnosis, and treatment of many other diseases). However, the yeast example tells us that new, rapid-genome-sequencing methods, even when coupled with profiling of the expression of our genes, will not be the end of the story. It is certainly true that in certain cancers, single genes can be mutated and that this has led to targeted drugs that block the effect of the mutation and extend life. Nonetheless, my intuition is that in most cancer, and most disease generally, the transformation of medicine will be far more challenging. After all, we and our cells have been evolving for billions of years. We are magnificent but almost unimaginably complex molecular symphonies of structure and function, and cannot be described as a collection of disconnected facts. These challenges needn't frustrate us. Instead, they should further drive us to imagine and experiment, using the power of science not only to ultimately transform medicine but, on the way, to offer context and meaning to our lives.

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