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By Richard Gallagher

Stumbling Towards Nirvana

The promises of personalized medicine have failed to materialize. That may be about to change.

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Several years ago, Francis Collins, current director of the National Institutes of Health, described the coming era of personalized medicine as “medical Nirvana.” It’s a compelling vision, one that I fervently hope will be achieved. But it is taking such a long time to gain the necessary enlightenment, that it sometimes appears that this particular Nirvana is a fantasy. Where do things stand today?

Let’s remind ourselves of the three-part promise of personalized medicine. First, everyone’s genome will be sequenced cheaply and the sequence will be interpretable, and predictive. Second, the bulk of a person’s anticipated medical problems, discerned by analysis of the sequence, will be avoided by genetic, lifestyle or therapeutic means. And third, where a disease has to be treated, it will be done with medicines that are exquisitely tailored to both patient and ailment. No risk, no mess, no problem.

The reality (to date) has been dramatically different.

The $1,000 genome may soon be with us and it will be an incredible technological achievement. But not necessarily a great medical one. It won’t even be close to useful if interpreting the sequence costs $10,000 a go, and/or if the interpretation isn’t exhaustive. Complex genetic diseases involve large numbers of genes each with a small effect, making it difficult to assess the risk of any particular variant. On top of that, the gene products interact with, and are modulated by, environmental factors. And on top of that, what we currently define as a single disease may not be that at all: It may be a heterogeneous collection of rare disorders.

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The genome itself presents a moving target as well. For instance, copy number

variations (CNV)—segments of DNA that appear in different numbers in different genomes—are not uncommon. Recently, microdeletions and microduplications that alter copy number at a particular locus have been associated with autism (*J Med Genetics*, Sept 24, 2009, epub ahead of print). These changes in the patients' genomes are not found in either parent. In fact, since the genome sequence varies somewhat from cell to cell, our bodies are a patchwork of highly related but nonetheless different genomes. Capturing this complexity requires multiple technologies. This is not to say that no advance has been made.

Genome-wide screens are providing a shortcut to understanding the mechanisms of disease without the need for understanding complex biochemistry or physiology.

Pharmacogenomics, too, is making valuable progress. This is the correlation of genetic variation with drug efficacy—or toxicity. The latter is important since adverse drug reactions account for 7% of all hospital admissions in the United States. Approximately 10 tests have come on the market to date, allowing patients to be divided into responders or nonresponders to different drugs. All are simple SNP tests but they represent a significant milestone, and the arrival of multigene tests is just a matter of time.

Pharma insiders also see pharmacogenomics as a boon, believing that it can be used to rescue drugs that have failed due to toxicity or lack of efficacy. The argument is this: Use genetics to discriminate a responsive, treatable patient group from nonresponders or adverse responders and you will have a viable drug on your hands. Turn to page 61 to meet some of the drug candidates that pharmacogenomics is currently rehabilitating.

The other commercial application—Direct-to-Consumer genotyping—isn't a success. A handful of companies continue to provide information on ancestry (whimsical), findings on traits (trivial), and a little advice on disease risk. They need time for research to turn them into a genuinely useful service, and Andy Warhol's aphorism, "buying is much more American than thinking," may see them through.

Getting back to a higher plane, Nirvana is the antithesis of ignorance. And dispelling ignorance of disease is progressing. So far we've stumbled forward a little on the road to personalized medicine, but it looks like the pace towards Nirvana is about to pick up.

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