Skirmishes, Uncertainties, and Great Promise: Robert Green on Precision Medicine

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In an afternoon keynote at the HIMSS Precision Medicine Summit in Robert Green of Brigham and Women's Hospital ostensibly wanted to discuss "where we're at and where we're going" with the use of genomics. His speech, however, revolved around various uncertainties at its core.

Green is quite the expert on the power of genomics and their head-spinning ethical questions. He headed up the American College of Medical Genetics and Genomics group that originally identified and published the ACMG 56 (now ACMG 59), the list of alleles heavily linked to various cancers.

Early in his speech today, he ran through what he perceived to be the six major current uses of genomic analysis, including the diagnosis of rare conditions and prenatal screening. He called the effort to develop targeted therapies and limited pharmacogenomics for cancer "arguably the most salient, novel technology that's affecting medicine right now.

Newborn sequencing along with expanded pharmacogenomics, expanded carrier screening, and more prenatal sequencing all hold the most near-term potential in genomics, in Green's view. In the long term, genetic editing and multi-omics become more feasible.

Also coming in the future of genomics, according to Green? A battle.

"I think we are going to have a lot of skirmishes and maybe even a war regarding population screening. We are pitting the enthusiasm of the futurists and the clinical perspective of those facing a patient in front of them… against the public health perspective that says 'be careful what you screen for.'" That clinical perspective, Green says, worries about downstream impacts and exploding costs.

"The major obstacle from where I sit to the implementation of genomic medicine today," he said, discounting costs and lack of physician familiarity and understanding, "Is the absolute lack of clinical utility data." There is certainly a lot of clinical utility theory, but theory does not convince insurers to cover tests and interventions or major institutions to endorse them for standard practice.

"Unit we can demonstrate clinical utility in ways that satisfy these groups, I think genomic medicine is stuck knocking on the door."

For green, the key issue is penetrance. In his words, "the probability that if you carry a mutation that you will develop that disease." It's universally known that BRCA1 increases breast and ovarian cancer risk, but there is no consensus across populations as to how much. When you get into less-studied variations and diseases, the picture is even less clear.

"The databases are incomplete, sometimes they're even wrong," he said.

The interplay between variation presence and symptoms also might change how medicine perceives the diseases themselves. He used the example of a patient with a variant that indicates cardiomyopathy, but relatively normal heart thickness.

"A year later it's still normal but it's grown more than expected for a year: do you have a phenotype or no? You don't have cardiomyopathy per se, only clinical criteria. It's really going to challenge our notion of what it means to have a phenotype…is it the wall thickness, is it the sarcomere abnormalities, is it the RNA expression? What exactly is the pheno?" he asked.

The great uncertainty of it all, Green was quite up front about for a man who directs a sequencing project (Harvard and Brighham and Women's Genomes2People program), was dramatic: "Is genomic information toxic?" he pondered. "Is the information itself bad for you?"

The question affects countless research projects in the sequencing world, looking to gather vast amounts of genomic data to improve their understanding, but also posed with the question of whether or not to divulge potentially-worrisome findings, like the presence of ACMG 59 variations, to patients in that aggregation process. One's stance on the return of genomic results is "like a Rorschach," according to Green.

In Genomes2People's MedSeq Project, for instance, they found that 92% of people carry at least one of over 4,600 disease-associated variants, and 21% of people carry a Mendelian risk variant. The majority of people had not developed whatever the conditions associated with those variants were, however. The full results of that study will be published coming in *Annals of Internal Medicine* later this month.

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