

The dark matter of personalized medicine: Non-genetic variation

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Abstract

Personalized medicine in its current iteration was developed with the goal of making an individual's genome sequence a source of useful, usable information. However, genome-based decisions require more data, an under-appreciated fact in a world where genomic sequencing is becoming increasingly more prevalent. The genotype of an individual is necessary, but not sufficient, for our understanding of how our genome interacts with our environment to translate into phenotype. For example, the variability in how genetically identical cells respond to the same stimulus is a universal feature of biological systems that limits treatment effectiveness.¹ To realize the promise of personalized medicine fully, we need to understand this variability. This requires a model that accounts for the variability observed within individuals in the human population. Here we outline the need to 1) understand (predict) how cell-to-cell variation impacts treatment outcomes, and 2) identify methods to modulate this variability to maximize treatment effectiveness.

When genomic sequencing becomes entirely common, what's next? Within the next decade, many humans with the resources to do so will have their genome sequenced. This information could provide the individual and their doctors with detailed disease risk profiles, drug sensitivity predictions, and recommendations for maximizing wellness. The vision that powered the initial sequencing of the human genome may be realized.² The ideal near term future is clear: billions of individual human genomes leveraged into accurate and actionable predictions, leading to longer, healthier lifetimes.

Much remains to realize this scenario—there are numerous well-documented limitations that need to be overcome for scientists to deconvolute the genome into significant components, random components, and everything in-between. These limitations range from healthcare system costs to the challenges of inferring the role of genetic variation in complex traits.^{3,4} There is also a concern of selection bias, where the genetic variation among large and wealthy demographics are overrepresented, leading to an underestimation of total genetic variation in humans.⁵ For the purposes of this discussion, we assume these are difficult but tractable problems that can be solved over the next decade.

Here, we restrict our discussion to the consequences of cell-to-cell variation within the individual and how it pertains to personalized medicine. We suggest that characterizing the cell-to-cell variation in response to drug treatment across a large population of individuals is an essential, overlooked principle for predictive modelling of treatment outcome. Further, we highlight the potential for treatments that modulate the variability of the biological system for maximizing beneficial treatment outcomes and patient wellness.

The genome is only a subset of the actionable chemical information that a human can provide. Genetic variability holds special standing in personalized medicine. Due to the relative permanence of the information it contains, the genome is an obvious place to look for predictors of disease, drug responsiveness, and wellness. It is convenient to correlate one or more individual genetic variants with a disease or health outcome across an otherwise diverse population.

This concept was initially validated in the pilot phase of the 1,000 genomes project that demonstrated the average human walks around with at least 50-100 disease-implicated genetic variants.⁶ This finding has since been greatly extended with the recent deep sequencing of 10,000 human genomes, observing an average of approximately 57 single-nucleotide variants per kilobase.⁷ Knowing one's genetic information is already actionable today, in that it allows for the patient and medical practitioner to establish treatments to curb or prevent premature health loss. Commercial services may be used to identify risk for Parkinson's disease, late-onset Alzheimer's, celiac disease, and others. Over time, it is possible the scientific community will extract all the actionable knowledge out of our genomes. What possibilities exist beyond this? In principle, any differences in the chemical identity of an individual, even beyond genome variants, that exist long enough to be both measured and acted upon could inform individual treatment.

To identify which parts of this information are valuable predictors of treatment outcome, we and others are attempting to quantitatively measure the cell-to-cell heterogeneity in drug response across a large population. We take an inventory of the cell's contents immediately before and after drug treatment, and look for common differences. At present, this process is prohibitively complex and too costly to use on an individual basis. We therefore leverage the simpler and more resource-efficient discovery system, budding yeast. In this pared-down model of human biology, less time, money, and human energy are required to test a biological hypothesis. We can measure a single cell's reaction to each of a few thousand drugs across thousands of genetically identical cells and provide a complete picture of the non-genetic variation in drug response in this biological system. Thanks to the extensive evolutionary conservation between yeast and human, and by leveraging previously developed techniques, we can extend this to a panel of thousands of biomedically relevant genotypes in order to understand how genotype affects non-genetic variation.^{8,9} This will allow us to learn which non-genetic elements of the cell's chemical identity are useful predictors for a given treatment.

With a detailed understanding of how cell-to-cell variability impacts the response to treatment, it may be possible to design drugs that cause less of a variable response. 'Combination therapy', involving a drug targeting the mechanisms that underlie cell-to-cell variability with another that is a disease-specific treatment, should

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lead to a more predictable, overall more effective, response.¹⁰ A promising example of this in practice is the sensitization of cells to tumor necrosis factor-related, apoptosis-inducing ligand (TRAIL). Co-administering Sorafenib (among others) reduced the variability in the timing of cell death, demonstrating that co-drugging may reduce cell-to-cell variability in drug response.¹¹ Drugs that target the cell-to-cell variability pathways are also less likely to suffer from the dose-dependent limits of monotherapy.¹²

The large-scale characterization of human genetic variation has demonstrated that our genomes are useful predictors of treatment outcome. In the years to come, as many more genomes are sequenced, the predictors we already have found will be improved, and new predictors presently limited in power will become actionable. The next challenge will be finding a means to predict how the non-genetic component of variation in cellular response will impact treatment outcome. There has been much work describing the processes and types of chemical changes in a cell that outlive a single cell-cycle: DNA methylation, nuclear organization, protein post-translational modification (particularly histones), inheritance of nuclear and cytoplasmic RNA species. However, what features can generally be manipulated to maximize positive outcomes during treatment are still unknown.

The future of personalized medicine will greatly benefit from identifying which mechanisms drive the variability of responses to a given treatment. We suggest that studying cell-to-cell variability within the individual, across a large population of individuals, will identify many drivers of non-genetic variation. Developing drugs that target these drivers will then allow all of us to alter non-genetic variation in our favour. One of the principle maxims of personalized medicine may be achieved: the right drug, at the right dose, at the right time, for each individual.

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