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Only Connect:

Personal Genomics and the Future of American Medicine

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Abstract

Access to one's own complete genome was unheard of just a few years ago. At present we have a smattering of identifiable complete human genomes, but the coming months and years will undoubtedly bring thousands more. What will this mean for the practice of medicine in the US? No one knows, but given the remarkable drop in the cost of DNA sequencing over the last few years, it seems a safe bet that within the next decade, primary care physicians will order patients' whole genome sequences with no more fanfare than they would a complete blood count. But the challenges of transforming that easily accessible information into cost savings and better health outcomes will be daunting. Obviously, we lack interpretive abilities and phenotypic information commensurate with our skill in amassing DNA sequences. Worse, we have exacerbated these problems by failing to embrace the increasing ubiquity of genomic information, the populace's interest in it, and its relevance to virtually every medical specialty. The success of personal genomics will require a profound cultural shift by every entity with a stake in human health.

"The future is the worst thing about the present."

—Gustave Flaubert¹

Whatever the ultimate fate of healthcare reform in the US,² whatever the limitations of genome-wide association studies,³ whatever loopholes exist in the Genetic Information Nondiscrimination Act of 2008,⁴ whatever objections the medical establishment offers to the concept of the masses obtaining their genomic information,^{5,6} make no mistake: the genomes are coming. It is inevitable. In the last few years, sequencing costs have plummeted by more than three orders of magnitude.⁷ The recent announcement that the California startup company Complete Genomics Inc. was able to sequence complete human genomes for less than \$5000 in reagents suggests that the arrival of the mythical \$1000 genome will soon be at hand.⁸ The data thus far suggest that people want this information, even with serious and abiding questions surrounding its predictive value.^{9,10,11}

As I write this in early 2010, a handful of identifiable people have had their genomes sequenced at high coverage.^{12,13} I am one of them, having had my whole genome sequenced by David Goldstein's lab in 2009 and my partial exome (the 1% of the genome that codes for protein) sequenced as part of the Personal Genome Project (PGP).¹⁴ I would not presume to extrapolate my experience to a population-wide genome-screening model; the infrastructure attached to whole-genome sequencing remains too inchoate and is not yet scalable to whole populations. But my collected experiences of open-source genotype interpretation via SNPedia (www.SNPedia.com), direct-to-consumer genome scanning, participation in the PGP, and obtaining my own genome – along with 3 years of close observation of the burgeoning world of personal genomics – have, I hope, given me some insight into the requisites for personal

genomics to be applied, such that it can be more of a boon to human health than a drain on an already frail healthcare system.

Here, I discuss what I perceive to be some of the most significant challenges to integration of personal genomics into clinical medicine. I suggest some possible ways forward, though I am under no illusions that any path we choose will be easy.

Phenotypes at Large

In my view, a lack of detailed phenotypic data is the ‘elephant in the room’ for personal genomics, at least with respect to clinical utility. We have become highly skilled at aggregating genomic data, but our willingness to collect the phenotypic information we wish to associate with our reams of genomic information remains inadequate. And our lack of will has consequences: incorrect phenotyping means more samples are needed to achieve equivalent statistical power.¹⁵ Thus, a commitment to better phenotyping makes both scientific and financial sense.

In part, our reticence is understandable. When we visit our physicians, they examine us and ask us questions. They take measurements, order tests, whack us on the knees, and try to elicit what, if anything, is wrong with us. This is the time-honored art of clinical diagnosis, and we have yet to come up with a less cumbersome substitute for it. 23andMe, Inc., the most popular direct-to-consumer genome-scanning company, is attempting to carry out research via surveys of its customers.¹⁶ Self-reported data are hardly useless,^{17,18} but neither are they the same as a visit to a physician.^{19,20}

Perhaps the best exemplar of the do-it-yourself approach to phenotyping is PatientsLikeMe.com, which has constructed a sophisticated database that tracks members’ medical information and has actually led to peer-reviewed publications.^{21,22,23} But the PatientsLikeMe model, at least so far, is based on communities of people who share frank clinical diseases and have already been immersed in the healthcare system because of them.²⁴ PatientsLikeMe is an extraordinary achievement and, in my opinion, something to be supported and emulated. But if personal genomics practitioners are to realize their goal of *preventing* disease, they must bring the PatientsLikeMe approach to bear on the *healthy* among us. They must cultivate communities of well people who are willing to invest the time and effort to attend to their own phenotypes with the same exactitude as PatientsLikeMe members coping with chronic diseases.

Otherwise, with few exceptions, personal genomics has, in my estimation, dragged its feet with respect to phenotypes. The 1000 Genomes Project is collecting no trait data.²⁵ Nor, outside of surveys, are the personal genomics companies (to my knowledge). The DataBase of Genotypes and Phenotypes (dbGAP) includes de-identified phenotypic data submitted by individual investigators; de-identification has been criticized because it may impoverish phenotypic data in ways that open-consent platforms such as the PGP and PatientsLikeMe need not confront.²⁶ As of early 2010, the PGP relied on participants to submit their own medical information.²⁷ The hope is that more entities will collect such data prospectively, just as the UK Biobank is doing.²⁸

Obviously, phenotype collection is difficult and expensive. It cannot be automated easily and may require high-level medical expertise and clinical acumen. But it can be done. Pääbo and colleagues,^{29,30,31} in their extensive studies of the *FOXP2* gene in the mammalian lineage and its contribution to language, collected data on hundreds of distinct traits in mice.

Could a similar effort be undertaken in humans? I believe it could. Indeed, I would argue that this pressing need presents an opportunity for the medical genetics community to assert itself.

The late Victor McKusick called medical geneticists “the last generalists” (Rienhoff HY, personal communication). They have an appreciation for nuchal folds, bifid uvulas, and other esoteric signs and symptoms that most everyone else simply doesn’t and can’t share. If there is to be a Human Phenome Project, it will require dysmorphologists to assume center stage. My worry, as I discuss below, is that the cultural chasm between traditional medical genetics and the early-adopter community that has embraced personal genomics is simply too wide to realize the goal of widespread human phenomics.

Genomic Interpretation: Man’s Search for Meaning

Even with phenotypic data in hand, the extraction of clinically and/or personally relevant meaning from human sequences will be among the most daunting tasks. But interpretation is another obvious necessity.

Consider Alzheimer’s disease and the apolipoprotein E (*APOE*) gene. Two copies of the *APOE* $\epsilon 4$ allele are associated with a 10- to 15-fold greater risk of garden-variety late-onset Alzheimer’s disease.^{32,33} Robert Green et al.³⁴ found that many individuals at risk for Alzheimer’s disease were interested in learning their genotypes for the *APOE* gene. Participants in Green and colleagues’ REVEAL (Risk Evaluation and Education for Alzheimer’s Disease) studies^{35,36,37,38} who learn that they are *APOE* $\epsilon 4$ positive tend to recall this information more frequently, rarely regret their decision, and are more likely to change their health behaviors.

But *APOE* is exceptional in many ways. We have 15 years of population data on *APOE*. *APOE* $\epsilon 4$ is not deterministic, but its association with Alzheimer’s disease is powerful and robust. We know what it means, at least in probabilistic terms. What happens when individuals are presented with information pertaining to traits governed by many more weak alleles in many more genes coupled with environmental effects, as most seem to be?

In the near term, barring the discovery of more *APOE*-type loci, it might behoove us to focus initially on carrier status for traits transmitted in a straightforward Mendelian way. Indeed, at least one company has staked its future on offering customers exactly this sort of information.³⁹ But let’s not kid ourselves: even so-called ‘simple’ Mendelian disorders are fraught with complexity. Cystic fibrosis is modified by multiple loci.⁴⁰ Nearly 10% of patients with long QT syndrome are compound heterozygotes.⁴¹ Well over a thousand variants of unknown significance have been found in the breast cancer susceptibility genes *BRCA1* and *BRCA2*.⁴²

We therefore have our work cut out for us if we are to identify the phenotypic consequences of variants that are known or suspected to disrupt gene function:⁴³ nonsense mutations, insertions/deletions (indels), essential splice site disruptors, and large structural rearrangements, to say nothing of single nucleotide polymorphisms (SNPs) in noncoding regions. Fortunately, new software packages such as the freely available Sequence Variant Analyzer are designed to look for and assess these sorts of changes.^{44,45}

At the Ethical, Legal and Social Implications of Genomics (ELSI) Conference in 2008, Maynard Olson⁴⁶ said that until we amass thousands upon thousands of genomes, each individual genome will only represent another “just-so story.” Indeed, we are still in want of a global resource with widespread buy-in from the human genomics community dedicated to the transition from “story” to clinically useful fact. SNPedia is clearly a step in the right direction. The University of California at Berkeley’s Steve Brenner⁴⁷ has called for the creation of an even more comprehensive resource: a Genome Commons – that is, a public knowledge base of all human genetic variation and its effect, culled from databases and the scientific literature. Commenting on the publication of the Watson and Venter genomes and the minimal insights that have emerged from them, Brenner had the temerity to ask, “If the genome is so

revealing, why was so little revealed?”⁴⁸ We would do well to heed visionaries like him, George Church⁴⁹ and others, and begin to pool our resources, especially if many variants with the most salient effects turn out to be extremely rare.

Obviously, successful genome interpretation – and identification of functional variation in noncoding sequences in particular – will require more than new software and massive aggregation. It will ultimately demand a deep understanding of the underlying biology.

Treating Culture Shock

I have no illusions that we are all on the same page: genome scientists, clinicians, genetic counselors, personal genomics companies, pharmaceutical and diagnostics firms, regulatory agencies, funders, and last, but not least, patients and consumers. We are in the early stages of a revolution: there is already blood on the ramparts, and we should expect more.

Consider two additional examples. Warfarin is the most widely prescribed blood thinner in the world. Warfarin dosing is tricky: the therapeutic window is narrow, and the consequences of the wrong dose can be life threatening.⁵⁰ We have known that there is a genetic basis to warfarin response for more than 40 years;⁵¹ people respond to different doses as a function of their genotypes at multiple genes, three of which together account for 40 percent or more of the variation in dosing requirements.⁵² Clinical trials of genotype-guided dosing did not begin until a few years ago.⁵³ The US FDA approved a label change to include information on how genetic variation may affect response to warfarin in 2007.⁵⁴ Despite this recent movement, a cursory perusal of the literature betrays no signs of consensus.^{55,56,57,58} My point is not that genetic assessment of warfarin sensitivity should be a routine part of standard practice; there may well be compelling clinical and financial reasons why it should not be. But shouldn't we know by now? Warfarin pharmacogenomics is traditional clinical research at its most meticulous, perhaps, but also at its most plodding.

What about the other end of the curve, where new knowledge has been embraced by patients without much deliberation? In 2007, scientists at the University of Alberta reported that a common household chemical, dichloroacetic acid (DCA), shrank tumors in mice; DCA activates mitochondrial apoptosis in cancer and results in suppression of tumor growth.⁵⁹ Within weeks of the Alberta team's announcement, cancer patients were ordering DCA from chemical suppliers, distilling it to pharmaceutical grade, dosing themselves, and comparing notes online.⁶⁰ Side effects associated with DCA include pain, numbness, gait disturbances, liver failure, and peripheral nerve toxicity.⁶¹ This was self-experimentation in extremis – understandable, given the desperate straits of the patients in question, but probably not anyone's ideal of personalized medicine in action.

Both examples, in my view, get to the heart of one of the impetuses behind personal genomics that is frequently neglected: disappointing progress in the clinical applications of otherwise amazing science. The Human Genome Project was accompanied by assurances of a new pharmacopeia full of genome-based drugs.^{62,63} Alas, with rare exceptions in cancer, these have yet to materialize. And genome-wide association studies turned out not to reveal the treasure trove of strong, shovel-ready, disease-susceptibility variants we had hoped for,⁶⁴ although they may yet point us toward those variants.⁶⁵

Meanwhile, the medical genetics community's early reaction to personal genomics has included large measures of indifference, healthy skepticism, and outright contempt.^{66,67,68,69,70,71,72} If patients who have opted to engage with their own genomes are to be told by their primary care physicians to “ask again in a few years,”⁷³ it is hardly surprising that motivated early adopters will look elsewhere for help and guidance. If we can routinely avail ourselves of flawed but broadly accepted clinical tests such as CA-125,⁷⁴ prostate-specific antigen,⁷⁵

and mammography,⁷⁶ then why should we tolerate being patronized for our more casual interest in, say, genetic mediators of our muscle type or propensity to develop rheumatoid arthritis?

There are some encouraging signs, however. The genomics community agrees on the need for scientific standards.⁷⁷ Direct-to-consumer genomics companies have started to partner with physicians.⁷⁸ In some cases, they are offering customers results whose clinical utility is not in doubt.⁷⁹ Sequencing instrument manufacturers are dipping their toes into the clinical realm.^{80,81} And patients have begun to force the issue by bringing commercial genome scan results to their physicians.⁸² Time will tell if the cultural divide can be bridged.

In the meantime, more can be done. One can imagine a ‘Head Start’-like initiative aimed at genetics and genomics education beginning in elementary school; DNA should not remain an abstraction until a child gets to university.⁸³ At the other end of the spectrum, medical students need both deeper and broader exposure to genetics and genomics. They can no longer subsist on curricula in which these subjects are treated as an antiquated backwater or, worse, an afterthought. If genetics education is dispensed with after the first year of medical school, it is of little use by the third.⁸⁴ Similarly, if the focus remains on rare, highly penetrant disorders and curricula fail to highlight the clinical relevance of genetic medicine to primary care,^{85,86} the knowledge gap will only widen. These are serious problems, but eminently solvable ones.

For their part, dysmorphologists should not be allowed to hide their collective light from science students and their basic scientist colleagues. Indeed, dysmorphologists and molecular geneticists must exist within the same bodies in ever increasing numbers. Only then will the Human Phenome Project be realized.⁸⁷ But to accomplish this type of integration will require financial, professional, and lifestyle incentives: geneticists should be rewarded for their career choices, not punished.

The ranks of genetic counselors need to grow as well, and this too will require a culture change. Formal genetic counselor education began in 1969.⁸⁸ So why did it take 38 years for the American Medical Association to add a new Current Procedural Terminology® (CPT) code to allow for billing and reimbursement of ‘Medical Genetics and Genetic Counseling Services’?⁸⁹ My hope is that after four decades on the front lines, genetic counselors’ ‘quiet revolution’⁹⁰ will grow to a deafening roar.

Conclusions

One hundred years ago, E.M. Forster published his classic novel *Howards End*.⁹¹ In it, Forster implored us to “Only connect!...Only connect the prose and the passion, and both will be exalted...Live in fragments no longer.”⁹²

For personal genomics, the connections that remain to be made are many. I have tried to argue here that some are especially crucial.

We must connect genotype with phenotype, but cannot do so if we have not mined phenotypes with the same ardor we have committed to collecting genotypes. With phenotypes in hand, we must then make the genotype-phenotype connection manifest by taking a Talmudic approach to the genome: constant re-reading, interrogation, re-interpretation, and perhaps even re-imagination.

And we must somehow overcome our defensive and paternalistic instincts and allow that ‘amateur hour’ is here to stay – and recognize that this need not be a bad thing. Citizen science has a long history, as anyone who has counted birds for the National Audubon Society will attest.⁹³ Part of this will involve revitalizing the connection between patient and physician. If

we are to capitalize upon the “wikification of knowledge,”⁹⁴ then this relationship must be recast as a true partnership, where information and resources do not exist within immutable hierarchies but, rather, travel in many directions.

Finally, we must honor Dr. McKusick’s view of his own guild. Geneticists are indeed the last generalists. Perhaps, to paraphrase the Gospel of Mark (10:31), the time has come for the last to be first.

These are tall orders. But if personal genomics is to succeed, I believe that each must be addressed. No longer can we afford to live as fragments.

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