



Cutting the Gordian Helix — Regulating Genomic Testing in the Era of Precision Medicine

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In his 2015 State of the Union address, President Barack Obama announced a new Precision Medicine Initiative (PMI), a national investment in research on approaches to disease treatment and prevention that

take into account individual variability in each person's genes, environment, and lifestyle. In a recent Perspective article, Francis Collins and Harold Varmus sketched out initial ideas for the PMI research plans as envisioned by the National Institutes of Health (NIH).¹ But scientific progress alone won't guarantee that the public reaps the full benefits of precision medicine — an achievement that, as Collins and Varmus note, "will also require advancing the nation's regulatory frameworks."

Nowhere are such advances more important than in the regulation of genomic testing, which falls under the auspices of the Food and Drug Administration (FDA). As I've engaged in planning for the PMI over the past year (as cochair of the President's Council of Advisors on Science and Technology), I've been thrilled to see that the FDA — sometimes viewed as hidebound — has been exploring radical new approaches for cutting the Gordian helix in which genomic testing has been bound. The ideas are described

in a recent discussion paper that merits the attention of the biomedical community.²

The knotty problem is how to promote rapid innovation while ensuring safety and efficacy. Gene discoveries are pouring out of laboratories: scientists have now identified 3600 genes for rare mendelian disorders, 4000 genetic loci related to common diseases, and several hundred genes that drive cancer. Firms from Boston to Silicon Valley are eager to help physicians, patients, and consumers use this knowledge.

Yet there are serious causes for concern. Genetic discoveries are often devilishly hard to apply in practice: Which mutations in a disease gene are actually damaging, and which are harmless? Are

variants reported to increase disease risk from 8% to 8.5% clinically meaningful — especially if the study hasn't been reproduced?

Troublingly, some firms are already peddling genotype-based pronouncements about whether a child is at significantly increased risk for suicide or autism, or about which treatments will most benefit a particular person with mental illness. Such claims are not harmless and may be quite dangerous. The firms often don't even disclose which genetic variants inform their predictions, let alone reveal the underlying evidence base. As far as I can see, many of these claims lack meaningful support in the scientific literature. Moreover, some laboratories fail to adhere to high standards. Most testing laboratories are scrupulous and careful, yet they are still struggling to provide clinically meaningful and understandable results based on a complex and rapidly evolving evidence base.

How can we encourage rapid innovation while ensuring patient safety? By law, the FDA must evaluate diagnostic tests for both analytic validity and clinical validity. For a gene-based test, this assessment comes down to two questions: Does the test accurately read out a targeted set of DNA bases in the human genome? Does the targeted set of DNA bases provide meaningful clinical information?

A narrow interpretation of the FDA's regulatory framework might lead to a *reductio ad absurdum*. Separate analytic studies might be required for each of the 3 billion nucleotides in the human genome, and each company that seeks to provide *BRCA1* testing

for predisposition to early-onset breast and ovarian cancer might be required to provide its own data package supporting the association.

Refreshingly, the FDA's new discussion paper floats — seeking comment without formally endorsing — the possibility of a more elegant approach, with the potential for higher-quality tests and faster approvals.

First, the massive amounts of data produced by “next-generation” sequencing can be a great asset for confirming analytic validity. The scientific community has accumulated extensive experience, from tens of thousands of samples, about the vast majority of the genome that can be reliably sequenced with current technology, as well as about the genome's dark alleys, where complex duplications and rearrangements lurk. Moreover, whole-genome sequencing of individual samples typically covers each nucleotide an average of 30 times. Ideally, software programs could be developed (and continually improved) that could perform validation tests on new sequencing devices and internal consistency checks on each individual sample.

Second, the scientific community has launched pilot efforts to systematically sift the genetic evidence and create reliable databases of the genes and genetic variants underlying disease. A flagship example is the NIH-funded Clinical Genome Resource (ClinGen) project, which gathers and curates data about the strength of relationships among genes, variants, and diseases.³ If such efforts were scaled up, they could provide rigorous — and regularly updated — public data-

bases for all key clinical needs. In principle, the FDA might offer a “safe harbor,” whereby sponsors whose genomic tests used interpretations that are consistent with recognized databases would not need to submit additional validation. (At the same time, sponsors would still be free to file applications seeking approval for tests based on other interpretations.)

In fact, the FDA has already taken small but significant steps in this new direction with its 2013 approval of Illumina's MiSeqDx sequencing platform and its diagnostic application to cystic fibrosis, based on a database of cystic fibrosis mutations created and curated by the research community.

Fleshing out these ideas will require a lot of work. As a first step, the FDA has convened a meeting in Washington in late February to gather input about alternative approaches. But for the first time, there is cause for optimism that a new framework can unleash creativity in the marketplace without compromising safety.

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1. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med* 2015;372:793-5.
2. Food and Drug Administration. Optimizing FDA's regulatory oversight of next generation sequencing diagnostic tests — preliminary discussion paper (<http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM427869.pdf>).
3. ClinGen, Clinical Genome Resource home page (<http://clinicalgenome.org>).

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