Genetics inMedicine | COMMENTARY

Returning pharmacogenetic secondary findings from genome sequencing: let's not put the cart before the horse

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Whole-genome and whole-exome sequencing are taking off in health care. DNA sequencing was introduced to enable the molecular diagnosis of congenital disorders and rare syndromes, followed by several studies that explored the introduction of sequencing in various clinical settings.[1,2] Given the role of DNA in many diseases and outcomes, it is understandable that there is research interest in the secondary use of sequencing data and in the preemptive sequencing of healthy individuals in the event that DNA data are needed for a later medical decision.

Expectations regarding the impact of DNA sequencing in health-care practice are high. Many researchers have already investigated the expectations, views, and attitudes toward receiving (secondary) findings from sequencing among African Americans[3] and non-African Americans[4]; among genetic,[5] pediatric,[6] primary care,[7] and nonmedical health professionals[8]; and about sequencing in patients with Lynch syndrome[9] as well as newborns[10] and children.[11] Several studies went beyond views and addressed intentions,[12] knowledge, awareness, and understanding[13]; whereas others focused on the practical aspects of how to integrate sequencing in health-care practice[14]; how to deliver the service[15]; how to prepare different health professionals such as nurses[16] and genetic counselors[17] for their role in the delivery; how to design the patient report[18]; and how to handle informed consent in adults,[19] children,[20] and in families with genetic disease.[21] We already have a glimpse of the usefulness[22] and cost-effectiveness of returning secondary findings.[23] All in one year.

The study by Nishimura and colleagues[24] in this issue of *Genetics in Medicine* is similar. It addresses pharmacogenetics (PGx)—perhaps the single category of secondary results that has been most trumpeted for potential clinical utility. Nishimura and colleagues present proof of concept on how alerts for secondary PGx findings from genome sequencing can be automated in electronic health records. According to the authors, "incidental findings can be used to generate decision support alerts, [but] substantial resources are required to ensure that each alert is consistent with rapidly evolving pharmacogenomics literature and is customized to fit in the clinical workflow unique to each incidental finding." Stated very simply, and slightly skeptically, their study showed that alerts for secondary PGx findings *can* be programmed but that we do not really know *what* to program.

The authors' conclusion reveals that there were two challenges in their study: can we technically program alerts for the return of secondary pharmacogenetic findings into electronic health records, and do we know how to identify those findings that are worth returning? The first question is not a scientific question but a technological one, and it probably has a very simple answer: yes, we can. If we can program bionic eyes and driverless cars, it seems highly likely that we can program straightforward, but likely context-dependent, alerts into an electronic health record system. The authors were able to produce alerts, 49 in 54 patients, but they did not comment on whether these alerts were correct (did the alert return the right information?), relevant (was the patient described drugs related to the reported pharmacogenetic association?), and useful (would such a change actually benefit patients?).

The second question is the real challenge: do we know what is worth returning? Well, not really. There are a handful of pharmacogenetic associations that affect drug response or safety beyond doubt, such as *HLA* for abacavir and *CYP2D6* for codeine,[25,26] but for most others there is at least substantial doubt about the utility of testing and even the robustness of the pharmacogenetic association. For the list tested by Nishimura and colleagues,[24] 7 of 11 variants (Table 1 in their article) are recommended by the Clinical Pharmacogenetics Implementation Consortium, of which only two also are recommended (but not required) by the US Food and Drug Administration.[27]

The authors are well aware of the ambiguity about what to return and argue that "substantial resources are required to ensure that each alert is consistent with rapidly evolving pharmacogenomics literature." The ambiguity equates a fundamental scientific question: when do we have enough evidence that we can conclude a pharmacogenetic association is true? And is it true that the evidence is changing rapidly?

Science is a process in which evidence typically accumulates through the synthesis of individual studies. In the classical approach these studies aim to falsify a hypothesis by attempting to demonstrate that it is not true. For example, the

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null hypothesis specifies that there is *no* association between a genetic variant and drug response. Every valid attempt in a methodologically sound study with sufficient statistical power that would fail to show no effect, and hence reject the null hypothesis, would make it more likely that the alternate hypothesis (i.e., that there is an association) is true. While the existence of an association can never be proven with certainty, at some point the accumulation of evidence can be evaluated as strong enough to conclude the presence of association.

A more fundamental point, however, is that even if a statistical correlation exists, say between a PGx variant and drug levels, this remains a far cry from establishing that such an association has any clinical relevance. Indeed, given the number of factors that influence drug efficacy and adverse reactions, any given PGx variant, regardless of the existence of a statistical correlation, will not necessarily matter in any meaningful way from a patient's perspective. This is illustrated robustly by recent work demonstrating that PGx guidance for warfarin dosing, long a poster child for the PGx field, simply does not matter when using this agent.[28,29]

Thus, while many associations are suggested by ongoing studies, not all remain statistically significant after replication studies, and few reach a level at which clinical implementation is warranted. Thus, the notion, suggested by Nishimura et al.,[24] that substantial resources are required to keep their alerts up to date is questionable. In reality, those resources would be far better used to determine what PGx associations (probably few, given the track record thus far) may actually improve patient outcomes. The responsible approach to the introduction of pharmacogenetic testing, or to the use of genetic data when collected preemptively, is to wait until the scientific evidence is robust enough to warrant its use. This advice holds as well for studies that examine people's attitudes, preferences, and intentions; how to design bioinformatics pipelines; and the design of counseling services and informed consent. Such studies will be needed but are meaningful only when it is clear what genetic tests should ultimately be introduced in practice.

Finally, we should also not be seduced by the facile notion that if one engages in whole-exome sequencing and generates secondary information (such as PGx data), that such information is "free" and now ripe for clinical application. Whether clinical information is initially generated at high cost, low cost, or no cost is beside the point. The clinical use of information that does not improve patient outcomes just because it is "free" ignores the fact that the inappropriate use of medical data has substantial downstream costs in terms of both patient well-being and money. Moreover, opportunity costs are very real in medicine; the inappropriate use of data to guide clinical decisions inevitably precludes more important expenditures of time and resources in patient care.

It is understandable that the potential of PGx to improve patient care has generated excitement. The notion that we could guide the use of drugs through genomic information is tantalizing. But unfortunately, that vision remains far from realized for the vast majority of medications after enormous expenditures of time and money. Given that after many years of effort very few examples of PGx application have shown much promise for actually improving patient outcomes, we should recognize the likely reality that the role of PGx guidance will be limited to relatively few agents.

We do not propose to thwart scientific progress, but, rather, to simply advocate for spending precious time and resources wisely. The appropriate first steps before introducing preemptive sequencing into the routine clinical arena is to demonstrate clinical validity and at least a reasonable suggestion of clinical utility.[30] So far, for the vast majority of pharmacogenetic tests, the evidence lags far behind.

DISCLOSURE

The authors declare no conflict of interest.

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