Is there a need for PGxceptionalism?

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In a recent commentary in *Clinical Pharmacology and Therapeutics*, Altman[1] declares that the implementation of pharmacogenomics (PGx) "requires that we separate it from other elements of genomic medicine." He argues that PGx tests "need only reach reasonable expectations of *noninferiority* (compared with current prescribing practices) to merit use." In his view, the implementation of PGx is less challenging than the use of genomics for estimating disease risk and prognosis, because genetic tests for drug response phenotypes offer better explanatory power and less risk for discrimination or misinterpretation. He also believes that cost-benefit analyses for PGx are not necessary because "genotyping is asymptotically approaching no cost" and positive test results are unlikely to lead to "spiraling follow-up test costs."

We, too, are enthusiastic about the prospects for PGx, but we see no reason why its successful integration into practice should require an exception from the principles of evidence-based medicine. The factors cited above do not distinguish pharmacogenomic tests from other genetic or nongenetic tests used to direct interventions in practice. "Genetic exceptionalism"—the concept that genetic information is unique and requires special protection—was first invoked in relation to health policy issues such as privacy and insurance discrimination. After years of debate, many researchers and practitioners have concluded that genetic information should not be treated differently from other personalized medical information.[2] Recently, Evans et al.[3] introduced the term "reverse genetic exceptionalism" to describe the premature embrace of genetics in healthcare and disease prevention. The idea that genetic information is different and therefore merits a pass when it comes to evidentiary standards (for example, because it has personal utility[4]) has been a hotly discussed topic, especially with respect to personal genomic tests sold directly to consumers.[5]

We should demand the same level of evidence for PGx that we require of all test-driven interventions in terms of analytic validity, clinical validity, and clinical utility for each intended clinical scenario.[6] Premature implementation of PGx testing to guide prescription choice could raise costs by driving the use of more expensive alternative drugs. It could also cause harm by narrowing the field of agents which a patient might benefit from. Randomized clinical trials (RCTs) are widely recognized as the gold standard, and although they may not be needed for all PGx or other tests, noninferiority trials are not always an obvious substitute. First, the goal of such trials is to compare an existing intervention with a proposed alternative that offers potential advantages, such as lower cost or simpler administration. When a PGx test supplements rather than replaces existing practice, its added cost must be evaluated against potential benefits and harms. No medical test is cost-free; even if the cost of genotyping fell to zero, PGx tests would be associated with facility, personnel, and administrative costs. The methods of noninferiority trials also introduce particular challenges in conduct and interpretation.[7] For example, noninferiority trials may have to be larger than RCTs that are designed to demonstrate superiority. Biases that tend to dilute differences between groups in a traditional RCT are conservative or "biased toward the null"; however, in a noninferiority trial, such biases tend to favor the alternative hypothesis of noninferiority, introducing type 1 error. Because of these methodologic concerns, an extension of the CONSORT statement has recommended specific reporting standards for noninferiority trials.[7]

The EGAPP working group, an independent, multidisciplinary group commissioned by Centers for Disease Control and Prevention has tackled the challenge of evidentiary standards for genomic applications.[8] EGAPP working group reports on several genomic tests, including a few PGx tests, have concluded that there is "insufficient evidence" to support their use, generating some frustration. It should be noted, however, that their conclusions are based on transparent methods for assessing chains of direct and indirect evidence similar to those required by other evidentiary groups (e.g., the US Preventive Services Task Force,[9]) for nongenetic interventions. To address the "evidence dilemma" in genomic medicine,[10] Veenstra et al.[11] and Khoury et al.[12] have recently pointed out that not all "insufficient evidence" is created equal. For example, when clinical validity has been established, evidence from observational studies may be combined with modeling and decision analysis to make a provisional argument for clinical utility. Under these circumstances, a recommendation of "use with informed/shared decision-making" could perhaps be justified. Collecting more practice-based evidence for such interventions is important, and the US Center for Medicare and Medicaid Services "coverage with evidence development" program provides one approach.[13] An evidence-based process is essential for identifying PGx tests that are appropriate for this type of evaluation and determining what additional data are needed to measure their performance in practice.

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