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Clinical implementation of pharmacogenomics: overcoming genetic exceptionalism

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After over half a century of research, there are many examples showing that inherited genomic variation causes substantial interindividual differences in drug effects, and yet the clinical use of pharmacogenomic testing remains uncommon. In the decade since the sequences of the pooled genomes from a few individuals were made public, (1-2) only a handful of pharmacogenetic tests have been translated into clinical laboratory tests. With the recent adoption of genetic non-discrimination laws in several countries,(3) there are fewer legal arguments to be made for withholding genetic tests from medical records. Herein, we address some of the reasons underlying genetic exceptionalism as it applies to the slow adoption of pharmacogenomics, and concrete steps we are taking to combat this deficiency in clinical practice.

When making prescribing decisions, health care providers must integrate multiple types of information (e.g. age, concurrent medications, renal and liver function) that are helpful, yet imperfect. Pharmacogenomic information, like non-genetic variables, need not be perfect to provide useful information to the prescriber. Despite evidence linking pharmacogenomic variation with drug exposure, toxicity, and efficacy, there seems to be an excessively high bar to which many clinicians, regulators, and payors hold pharmacogenetic evidence.(4)

In our own practices, we have experience using several pharmacogenomic tests. Treatment of acute lymphoblastic leukemia includes thiopurines, whose metabolism, adverse effects, and effectiveness have all been linked to inherited polymorphisms in the *TPMT* gene.(5-7) The same group of patients experience periodic neuropathic or musculoskeletal pain; because nonsteroidal anti-inflammatory medications are best avoided due to their drug interaction profile, codeine is often the analgesic of first resort. However, the analgesic effectiveness of codeine is absent in the 5-10% of the population who cannot activate codeine because they inherited two inactive alleles of *CYP2D6*. (8) In adult oncology, some have begun testing for polymorphisms in the same gene, *CYP2D6*, as studies have demonstrated that tamoxifen-treated women with impaired *CYP2D6* enzyme activity cannot

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Conflict of interest statement

WEE and MVR have received patent royalty from *TPMT* genotyping tests. MPG is a named inventor (along with Mayo Clinic) in regard to nonprovisional patent applications regarding tamoxifen and *CYP2D6*; the technology is not licensed, and no royalties have accrued

fully activate tamoxifen and have a higher risk of breast cancer recurrence.(9) Thus, for several years, our groups have been testing patients for polymorphisms in *TPMT* and *CYP2D6*, and using genotype to adjust therapy.

This commentary is prompted by our prior experiences and by several new developments.

One of the impediments to adoption of pharmacogenomic testing is the fact that some prescribing decisions must be made emergently, necessitating the availability of pre-emptive genotype results. Moreover, even for pharmacogenetic examples which have led to FDA relabeling, (e.g. *TPMT* homozygosity and life-threatening myelosuppression after a thiopurine, (10) *HLA* genotypes and Stevens-Johnson syndrome after an anticonvulsant (11)), there is an “I’ll take my chances” bravado among clinicians, perhaps in a desire to avoid costs incurred with tests that will be negative in the vast majority of patients. However, a low-cost testing platform that focuses on clinically penetrant (even if rare) pharmacogenetic variants would allow for feasible up-front preemptive testing, accessible when needed. Indeed, dense arrays of hundreds of clinically-relevant pharmacogenetic tests can be completed for about the same cost as one or two send-out clinical pharmacogenetic tests. Thus, reduced costs of genotyping will soon change the balance to favor preemptive pharmacogenomic testing, even for rare polymorphisms.

What barriers to implementation of preemptive genotyping will then remain? If 225 pharmacologically-relevant genes are tested on an array, but only 2 genes are relevant to the current clinical situation, is it ethical or reasonable to cherry-pick the results for those 2 genes for transfer to the medical record and withhold results from the other 223 genes? Genetic tests have life-time long implications. Perhaps a future life-threatening drug reaction linked to one of those 223 genes could have been prevented had the result been placed in the medical record. The problem of how to handle findings that are currently considered “incidental,” but might in the future be highly germane, plagues many areas of medicine. (12) The conflicting interest of the patient, who often wants all possible useful results available, and the clinician, who frets over the liability of being held accountable for all 225 genes, raises the question of whose interests predominate in handling incidental results. Some novel practices are being tested, such as an “informed cohort” approach which places substantial responsibilities on patients to act as guardians of their own medical record;(13) however, many patients need clinicians to “step up” and decide the relevance of tests on their behalf.

Are clinicians ready to use pharmacogenetic information? One barrier is that many clinicians are unaware of the pathways necessary for drug activation or inactivation---much less how pharmacogenetic variation affects drug disposition. Furthermore, test interpretation requires an understanding of the limitations of which genomic variants have been interrogated and how gene duplication and deletion may complicate interpretation. This specialized knowledge must be constantly updated as scientific data change. Although clinicians want to understand the basis for modifying their prescribing, most will accept a system that provides bottom-line advice. At a minimum, clinicians need to be warned if a high-risk genotype collides with a high-risk drug prescription, a collision that could be detected by computerized decision support. Despite decades of promise, the use of

computerized decision support in medicine remains rare.(14) This support should account not only for hundreds of genomic variations, but also for the other imperfect non-genetic variables (patient adherence, diet, smoking, body size, organ function, and drug-drug interactions) that affect optimal prescribing. High-risk genotypes must be electronically linked to the action of prescribing, dispensing, or administering the affected medications in order to generate appropriate alerts at the moment the prescribing decision is made (i.e. preemptively), a practice we have recently incorporated into our own electronic medical records for some tests.

To address some of these barriers, the Clinical Pharmacogenomics Implementation Consortium (CPIC) has been formed (www.pharmgkb.org). This group will curate data on pharmacogenetic tests that are ready for clinical implementation now, and will update, annotate, and score evidence linking drug dosing decisions to genetic tests, and to address any incidental findings implications of the test. The Consortium will also share processes for the rational transition of pharmacogenetic genotypes from the laboratory to the clinic, thereby providing guidance for those who wish to implement clinical pharmacogenetic testing. CPIC will ultimately provide a source of peer-reviewed and practical recommendations for clinicians to use genetics when prescribing drugs.

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