American Society of Clinical Psychopharmacology Corner
J. Craig Nelson, MD, Editor

Do You Order Pharmacogenetic Testing? Why?

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The first question posed in the title of this article, whether pharmacogenetic testing should be ordered, arises with increasing frequency at psychiatric conferences and in discussions among peers. The second question, *why* to order it, is posed less often, apart from broad declarations that "pharmacogenetic testing can help guide treatment." How, exactly? And when? Seldom does the idea of pharmacogenetic testing incur the usual skepticism with which psychiatrists size up purported treatment advances. Perhaps this is due to high hopes that, despite its nontrivial cost, such testing enhances care and also demonstrates the biological underpinnings of our prescribing practices. While the ideals of personalized medicine are linked closely with pharmacogenetics, most notably in cancer, the enthusiasm with which many clinicians now embrace pharmacogenetic testing as a clinically useful tool, given the present state of knowledge, warrants a critical and dispassionate appraisal.

The proposition that genetics may play a role in drug response is tested at the molecular level by pharmacogenetics and at the macro level by examining familiality of drug response. Countless practitioners seize upon historical information that a patient's relative—however distant—"responded" to a particular treatment and conclude that a similar outcome is therefore expectable for the proband. Literature to support or refute this presumption is scant, with only a few notable exceptions: concordance rates of about two-thirds have been shown with lithium responsivity between bipolar probands and their affected first-degree relatives,[1] and similar concordance rates have been reported for antidepressant response to fluvoxamine among major depression patients and their affected first-degree relatives.[2] The paucity of data certainly does not negate the possible heritability of drug response, but rather serves as a reminder that assumptions about a genetic basis for treatment response are more speculative than factual.

Separate from the question of whether drug response is a heritable trait is whether drug effects can be predicted from single-nucleotide polymorphisms (SNPs) for genes involved in the presumptive neural circuitry associated with a given psychiatric disorder. Here too, data are lacking to establish that pharmacodynamic effects broadly constitute a genetically mediated phenomenon. Some authorities[3] point out 3 core considerations around pharmacogenetic testing: (1) analytic validity (eg, whether a test accurately detects allelic variants); (2) clinical validity (ie, whether a particular genetic profile causes clinically relevant effects); and (3) clinical utility (ie, whether testing results meaningfully alter treatment outcomes). The first of these issues is hampered in part because, except for the Roche AmpliChip CYP450 Test, no commercially available pharmacogenetic tests are approved or regulated by the US Food and Drug Administration. This article focuses mainly on the latter two of these concepts, along with testing intended to help predict drug benefits ("efficacy pharmacogenetics"[4]) versus adverse effects ("safety pharmacogenetics"[4]), particularly in major depression.

Evidence to support commercial claims that pharmacogenetic tests can identify treatment responsiveness is modest and indirect, stemming mainly from open-label, nonrandomized industry-sponsored studies showing improvements from baseline in symptoms, quality of life, or patient (or doctor) satisfaction, when clinicians are given results from a panel of pharmacokinetic gene variants (eg, cytochrome P450 [*CYP*]) and putative pharmacodynamic gene SNPs (eg, related to serotonin or dopamine receptor functioning).[5–7] Particularly given the many clinical, psychosocial, and other factors that influence depression outcomes, it is difficult to attribute drug response to genotype guidance when study designs lack sham-guidance control groups, information about actual medications and dosages, drug adherence, diagnostic standardization and reliability, possible ascertainment bias, control for confounding factors (racial, demographic, or clinical characteristics or cotherapies), or uniformity of study psychiatrists' experience and expertise. CYP2D6 poor metabolizers (PMs) have been shown from post hoc analyses in venlafaxine trials to have less robust improvement on depression severity scales,[8] although rating scales may not neatly differentiate physical symptoms of depression from adverse drug effects.

In major depression, a large meta-analysis found that the *l* (long) (versus *s* [short]) variant of the serotonin transporter gene (*SLC6A4*) only modestly predicted selective serotonin reuptake inhibitor (SSRI) response or remission, with caveats (findings applied to older white women with late illness onset).[9] Underpowered and unreplicated, findings from candidate gene association studies such as these are at best preliminary and lack generalizability. In far larger genome-wide association studies (GWAS) of depression, replicated findings of putative susceptibility loci that achieve genome-wide significance are virtually nonexistent. Indeed, pharmacogenomic GWAS for SSRI response in depression have yielded no findings of genome-wide significance (eg, Biernacka et al[10]). Clinicians who may be unfamiliar with such study design limitations in genetics are vulnerable to accepting manufacturers' claims at face value that a test will "double response rates" based on statistically nonsignificant findings from commercially sponsored, underpowered studies.

Current pharmacogenetic practice guidelines address pharmacokinetic more than pharmacodynamic considerations; they provide information about the likelihood of poor drug response in CYP2D6 or CYP2C19 ultrarapid metabolizers and a greater adverse effect burden among PMs due to decreased clearance.[11,12] They offer helpful suggestions about compensatory dosing adjustments for ultrarapid or poor metabolizers but make no formal recommendations to practitioners about whether and when pharmacogenetic testing should be ordered as part of routine care. Nor has its cost-effectiveness been demonstrated in the treatment of major depression.[13] On the basis of currently available data, the Centers for Disease Control and Prevention Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found "insufficient evidence to support a recommendation for or against use of *CYP* testing in adults beginning SSRI treatment for nonpsychotic depression. In the absence of supporting evidence,

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and with consideration of other contextual issues, the "EGAPP group discourages use of *CYP* testing for patients beginning SSRI treatment until further clinical trials are completed" (https://www.cdc.gov/genomics/gtesting/EGAPP/recommend/CYP450.htm).

The tides turn, somewhat, when discussion shifts from *efficacy* pharmacogenetics to *safety* pharmacogenetics. Genetically poor metabolizers of drugs that are substrates for CYP2D6 or CYP2C19 (about 5%–10% of whites and more variable numbers of nonwhites) are more susceptible to adverse effects. They may also poorly convert prodrugs that are metabolized by hepatic enzymes (eg, codeine) to their biologically active metabolites (eg, morphine). (However, most psychiatric prodrugs, such as lisdexamfetamine, become activated not by hepatic metabolism but by gastrointestinal or peripheral hydrolytic enzymes.) Does knowing the genotype of a "side effect–prone" patient, who might have a PM genotype, change their management? Perhaps, but would a clinician not simply use low doses in such patients and avoid potent inhibitors of their metabolic enzymes as a general rule? Moreover, poor drug tolerability is not fully explainable by genotype; in one study of venlafaxine for major depression, one-quarter of patients with normal ("extensive metabolizer") CYP2D6 genotypes resembled PM phenotypes, while adverse effects were 7 times more prominent in patients with normal than PM genotypes.[14]

Pharmacogenetic studies have *very provisionally* identified a handful of adverse effects that may be associated with particular candidate gene SNPs, which are possibly relevant (if replicated) for anticipating phenomena such as hyperprolactinemia or extrapyramidal effects from antipsychotics, nausea or sexual dysfunction with serotonergic antidepressants, and weight gain from atypical antipsychotics. The methylene tetrahydrofolate reductase gene (*MTHFR*) has a known functional polymorphism (C677T), coding for the enzyme needed to transport folic acid across the blood-brain barrier in order to enable CNS serotonin synthesis, but it is unknown whether oral supplemental L-methylfolate is "indicated" for MTHFR C677T poor or intermediate metabolizers—a hypothesis for which supportive data are preliminary[15] and unreplicated. If genetic variants contribute to adverse (or beneficial) drug effects, one must bear in mind that most such outcomes represent complex, non-Mendelian traits influenced by multiple genes that exert small effects. How much those effects account for observed pharmacodynamic outcomes, relative to the influence of nongenetic factors, remains unknown.

A handful of specific genetic variants have been identified that pose a significant hazard if left unidentified; most notably, an elevated risk for Stevens-Johnson syndrome from carbamazepine among certain Asian groups with the HLA-B*1502 genotype (accompanied by a manufacturer's boxed warning[16]). High iloperidone or valbenazine doses pose a greater cardiac risk for QT prolongation in unrecognized CYP2D6 PMs. The quest to identify genetic markers to predict clozapine-induced agranulocytosis (eg, Goldstein et al[17]) is ongoing.

A recent survey of ASCP members found that about one-third reported ever obtaining pharmacogenetic testing in at least 1 patient, most often to affirm what they already suspected about sensitivities to adverse effects; less than 10% felt that test results were useful to guide treatment.[18] Meanwhile, a systematic review of pharmacogenetic testing in psychiatry concluded that "antidepressant pharmacogenetics have not produced any knowledge applicable to routine clinical practice yet."[19(p62)] Like most if not all putative biomarkers in psychiatry, pharmacogenetics holds promise and importance mainly for translational investigators. As a research tool, it could help identify possible endophenotypes to refine nosology and diagnostics. In years to come, it could help define personalized medicine with the same aspirational optimism as in oncology. Until then, psychiatrists who want to be at the "cutting edge" might glean more from following the literature rather than their patient's genome panel.

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