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# Personalized Medicine in Psychiatry: Concepts for Bringing Associated Testing Into Clinical Practice

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In the current issue of *Mayo Clinic Proceedings*, Nassan et al[1] discuss pharmacokinetic pharmacogenetic prescribing guidelines for antidepressants as a template for psychiatric precision medicine. Personalized medicine is a concept that has been discussed for years in the medical literature and among the general public. Although often introduced as a recent innovation, in point of fact, physicians and other prescribers have always practiced personalized medicine by (1) selecting specific drugs for specific patients on the basis of a variety of factors (eg, personal or family history of response) and (2) individualizing the doses and schedules of administration (often titrated on the basis of efficacy or lack thereof and adverse effects). However, developments from the human genome projects and related molecular biology research have dramatically increased the ability to individualize medical treatments, particularly in fields of oncology in which new drug development has been based in part on being able to understand how specific cancers differ from normal tissue and then developing treatments aimed at those differences.

Such treatment parallels have not occurred yet in psychiatry, but expansion of individualized medicine paradigms is likely an inevitable development in this treatment domain as knowledge of the circuits involved in specific psychiatric illnesses becomes better defined. These advancements will likely involve the exploitation of genetic variants of regulatory proteins (eg, receptors) within neuronal circuits responsible for the manifestation of the illness (eg, negative emotional valence in individuals with specific forms of major depressive disorder [MDD]).

At the present time, the use of genetic testing in psychiatry is principally directed toward identifying variants in drug-metabolizing enzymes (eg, specific cytochrome P450 [CYP] enzymes) or genetic variants in pharmacodynamic targets (eg, the long vs the short form of the promoter region for the serotonin [5-hydroxytryptophan] transporter, which is the apparent mechanism of action of serotonin selective reuptake inhibitors [SSRIs] and one of the mechanisms of the serotonin-norepinephrine reuptake inhibitors [SNRIs]).

Clinicians should be aware that laboratories offering most genetic testing currently do not have to prove the efficacy or utility of the test results in diagnosing and treating diseases. Instead, they only have to have certification by the Centers for Medicare and Medicaid Services, according to the Clinical Laboratory Improvement Amendments (CLIA) standards.[2] CLIA-certified laboratories are required to document the analytic validity of tests that they offer—ie, the accuracy and reliability of the test in measuring a parameter of interest—but *not* the clinical validity or utility of those tests. Restated, to enter and remain in the marketplace, a CLIA-certified test simply needs to appropriately measure what it claims to measure.

With some exceptions, the introduction of a test does not require approval by the US Food and Drug Administration (FDA) as drugs do. The exceptions are when the test has been developed as a companion diagnostic or monitoring tool as part of the development of

a new treatment (eg, oncology). The reason that the FDA does not currently regulate the development of tests is that their charter mandate is restricted to determining the safety and efficacy of new treatments.[3] With that said, the lack of oversight by an independent and qualified entity such as the FDA means that the data collection and analysis supporting the new tests may be solely done by the entity whose viability depends on the commercial success of the test.

The thresholds above analytic validity are (1) *clinical validity*, which is the ability of a test to detect (a) a clinically meaningful measure, such as clinical response, (b) an adverse effect, or (c) a biologically meaningful measure (eg, a drug level or a change in the electrocardiographic pattern) and (2) *clinical utility*, which is proof that the test can reliably be used to guide clinical management and thus meaningfully improve outcomes, such as guiding drug or dosage selection. (Additional discussion of these concepts and other general issues about the regulations underlying the offering of genetic testing is available in another editorial that addresses some background information when assessing claims made by genetic testing companies.[4])

These aforementioned issues are of great importance to psychiatric practitioners and related health care professionals because psychiatry has had few laboratory tests specific to the diagnosis and treatment of patients with psychiatric illnesses and such testing is likely to dramatically expand over the next decade or more. Practitioners may be entering a "buyer beware" era in which for-profit companies increasingly bring their tests to the marketplace of routine clinical practice. For this reason, practitioners should be aware of what CLIA certification means as well as the difference among the 3 key concepts of analytic validity, clinical validity, and clinical utility.

As Nassan et al[1] point out, improved prescription of antidepressants is important because of the widespread use of these medications. It is particularly important when selecting the first SSRI or SNRI antidepressant for a specific patient. The reason is 2-fold. First, there is considerable overlap in the efficacy of the SSRIs and SNRIs. Second, a large percentage of patients with major depression (ie, approximately 45%) are not responsive to existing antidepressants, which all rely on mechanisms affecting biogenic amine neurotransmission (ie, serotonin, norepinephrine, and/or dopamine). The figure of 45% comes from the largest antidepressant treatment trial ever conducted by the National Institute of Mental Health—the Sequenced Treatment Alternatives to Relieve Depression (STAR*D)—which involved 4 sequential adequate trials of different biogenic amine antidepressants.[5] In that study, the likelihood of remission decreased precipitously with each sequential trial.[5] For this reason, psychiatrists and their fellow prescribers of mental health drugs often resort to various drug combination or augmentation strategies that often have variable levels of evidence to support their efficacy and safety.

The 45% of patients with MDD are currently outside the purview of existing genetic testing. To address this vexing clinical problem, a minimum of 2 advances are needed: (1) a test that identifies individuals with the biogenic amine antidepressant-nonresponsive form of MDD and (2) a treatment that works in such patients. The latter requirement harkens back to oncology, in which a companion diagnostic test guides the practitioner to the use of a treatment developed specifically for that type of cancer. I suspect that such drug development and companion diagnostics will occur during the careers of resident psychiatric physicians matriculating now.

The article by Nassan et al is an erstwhile attempt to take existing knowledge and apply it to existing therapies. As the authors specify, their goal—an admirable one—is to provide pharmacokinetic pharmacogenetic guidelines for antidepressants primarily metabolized by CYP2D6 and CYP2C19. Their algorithm is not prescriptive but instead a synthesis of the existing literature and a general guide. Because their research is based on a review of the literature rather than prospective studies, their algorithm does not meet the criteria for clinical validity or utility. Instead, additional prospective randomized studies would be needed to provide that level of evidence.

My suspicion is that such prospective research would not support the inclusion of fluoxetine and paroxetine in the algorithm proposed by Nassan et al because both of these drugs saturate and inhibit the CYP2D6


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enzyme under clinically relevant dosing conditions. As the authors point out, fluoxetine and paroxetine at a dose of 40 mg/d causes phenoconversion of the vast majority of normal (or extensive) metabolizers (ie, upwards of 95%) to phenocopies of CYP2D6 poor metabolizer status.[6,7] In fact, paroxetine is the first victim of its ability to inhibit CYP2D6 because its half-life at a single dose of 10 mg/d is 10 hours but increases to 20 hours or longer when 20 mg/d is administered to the attainment of steady state.[8,9] The change in half-life of paroxetine occurs because CYP2D6 has a high affinity but low capacity for the metabolism of paroxetine and becomes saturated as the concentration of paroxetine increases, leading to paroxetine's metabolism being taken over by a lower-affinity but higher-capacity enzyme, most likely CYP3A3/4. Taken together, these results strongly suggest that genetic variability in CYP2D6 is irrelevant to the concentrations of fluoxetine and paroxetine achieved under clinically relevant dosing conditions. Parenthetically, their propensity to cause CYP enzyme-mediated drug-drug interactions is a good reason to restrict the use fluoxetine or paroxetine to the rare instance in which their value outweighs the risk of CYP enzyme-mediated drug-drug interactions, which is an important concern for patients with major depression since they are often taking multiple medications because of their high incidence of comorbid medical illnesses.

In my opinion, the following conclusions can be made. Genetic and other laboratory (eg, inflammatory cytokines [not discussed in this editorial]) tests will increasingly be used in psychiatry over the coming years, and practitioners today need to understand the principles outlined here to be able to utilize these tools in an informed way in the treatment of patients. Nassan et al[1] have provided a review of the rationale for this inevitability and have presented an algorithm to aid in the selection of antidepressants for patients in whom the genetic information needed is already known with the aforementioned caveats.

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