Genetic and related laboratory tests in psychiatry: What mental health practitioners need to know

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Disclosure
The author serves on the scientific advisory board of Assurex Health, the developer and marketer of the GeneSight test.

There has been a significant upsurge in the development of new laboratory tests for use in psychiatric practice. In this Editorial, I answer salient questions about those tests for mental health practitioners—particularly those who prescribe psychotropic medications. The discussion is not exhaustive, and I do not review the pros and cons of any one company's tests.

What has been the history of the development of laboratory tests in the field of psychiatry?

During my almost-40-year academic medical career, I have been interested in the development and incorporation of laboratory tests into psychiatry.[1] This interest initially focused on therapeutic drug monitoring (TDM) and the genetics of drug responsiveness, with an emphasis on drug metabolism. In addition to TDM—which I have long believed is vastly underutilized in psychiatry—there have been many failed attempts to develop diagnostic tests, including tests to distinguish between what were postulated to be serotonergic and noradrenergic forms of major depression in the 1970s[2,3] and the dexamethasone suppression test for melancholia in the 1980s.[4] Recently, a 51-analyte immunoassay test was marketed by Rules-Based Medicine, Inc. (RBM), as an aid in the diagnosis of schizophrenia, but the test was found to suffer a high false-positive rate and was withdrawn from the market.[5] Given this track record, caution is warranted when examining claims for new tests.

What types of tests are being developed?

Most tests in development are pharmacogenomic (PG)-based or immunoassay (IA)-based.

PG tests examine single nucleotide polymorphisms (SNP) in genes that code for pharmacokinetic mechanisms, primarily cytochrome P450 (CYP) enzymes responsible for drug metabolism and P-glycoprotein, responsible for drug transportation. The next most common type of test examines pharmacodynamic mechanisms, such as SNPs of specific receptor genes, including serotonin (or 5-hydroxytryptophan [5-HT] transporter [SET or 5-HTT]) or the 5-HT2A receptor.

The fact that CYP enzymes lead the list is not surprising: These enzymes

and their role in the metabolism of specific drugs have been extensively studied since the late 1980s. Considerable data has been accumulated regarding variants of CYP enzymes, which convey clinically meaningful differences among individuals in terms of their ability to metabolize drug via these pathways. Individuals are commonly divided into 4 phenotypic categories: ultra-rapid, extensive (or normal), intermediate, and poor metabolizers. Based on these phenotypes, clinical consequences can be quantitated in terms of changes in drug concentration, concentration-dependent beneficial or adverse effects, and associated/recommended changes in dosing.

Research into the role of pharmacodynamic variants, however, is still in infancy and more difficult to measure in terms of assessing endpoints, with related limitations in clinical utility.

IA assays generally measure a variety of proteins, particularly those reflecting inflammatory processes (eg, various cytokines, such as interleukin-6).[6] As with pharmacodynamic measures, research into the role of inflammatory biomarkers is in early stages. The clinical utility of associated tests is, therefore, less certain; witness the recent study[5] I noted that revealed a high false-positive rate for the RBM schizophrenia panel in healthy controls. Nevertheless, considerable research is being conducted in all of these areas so that new developments might lend themselves to greater clinical utility.

(Note that PG biomarkers are *trait measures*, whereas IA biomarkers are *state measures*, so that complementary use of both types of tests might prove useful in diagnosis and clinical management. Although such integrative use of these 2 different types of tests generally is not done today.)

What does it take to market these tests?

At a minimum, offering these tests for sale requires that the laboratory be certified by the Centers for Medicare & Medicaid Services, according to the Clinical Laboratory Improvement Amendments (CLIA) standards (www.fda.gov/medicaldevices/device regulationandguidance/ivdregulatory assistance/ucm124105.htm). CLIA-certified laboratories are required to demonstrate the analytical 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. The fact that a test in fact measures what it claims to be measuring alone does not mean it has clinical validity or utility (see the discussion below).

Must the FDA approve laboratory tests?

No, but that situation might be changing.

Currently, only tests used in a setting considered high risk—eg, a test intended to detect or diagnose a malignancy or guide its treatment—requires formal FDA approval. The approval of such a test requires submission to the FDA of clinical data supporting its clinical validity and utility, in addition to evidence of analytic validity.

Even in such cases, the degree and quality of the clinical data required are generally not as high as would be required for approval of a drug. That distinction is understandable, given the type and quantity of data necessary for drug approval and the many years and billions of dollars it takes to accumulate such data. For most laboratory tests, providing the same level of data required to have a drug approved would be neither necessary nor feasible given the business model

underlying most laboratories providing laboratory tests.

What do 'clinical validity' and 'clinical utility' mean?

These are higher evidence thresholds than is needed for analytic validity, although the latter is a necessary first step on the path to achieving these higher thresholds.

Clinical validity is the ability of a test to detect:

- a clinically meaningful measure, such as clinical response
- an adverse effect
- a biologically meaningful measure (eg, a drug level or a change in the electrocardiographic pattern).

Above the threshold of clinical validity is *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.

Is the use of PG testing recommended? If so, in what instances?

Specific types of PG testing is recommended by the FDA recommended. The FDA has been incorporating PG information into the labels of specific medications for several years; the agency has a Web site (www.fda.gov/drugs/scienceresearch/research areas/pharmacogenetics/ucm083378.htm) that continuously updates this information. The involved drugs are in all therapeutic classes—from oncology to psychiatry.

More than 30 psychotropic drugs have PG information in their label; some of those drugs' labels contain specific recommendations, such as obtaining PG information before selecting or starting a drug in a specific patient. An example is carbamazepine, for which the recommendation is to obtain HLA testing before starting the drug in patients of Han Chinese ancestry, because members of this large ethnic group are at greater risk of serious dermatologic adverse effects, including Stevens-Johnson syndrome.

In other instances, the recommendation is to do the testing before increasing beyond a specific dose. Examples of psychiatric drugs whose labels contain such PG information include pimozide and iloperidone as well as citalopram. In the FDA-approved label, guidance is provided that these drugs can be started without testing if prescribed at a reduced recommended starting dosage range, rather than the full starting dosage range. The guidance on these drugs further recommends testing for genetic CYP2D poor metabolizer (PM) status of CYP2D6 or CYP2C19 in the case of citalopram and by extension S-citalopram before dosing above that initial recommended, limited, starting dosage range.

The rationale for this guidance is to reduce the risk that (1) patients in question will achieve an excessively high plasma drug level that can cause significant prolongation of intracardiac conduction (eg, QTc prolongation) and thus (2) develop the potentially fatal arrhythmia *torsades de pointes*). Guidance is based on thorough QTc studies that were performed on each drug,[7,8] which makes them examples of instances in which the test has clinical validity and utility as well as analytical validity.

To find PG labeling in the package insert for these drugs, visit: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

What about data for other tests that are marketed and promoted by developers?

Sometimes, there are—literally—no data on available tests beyond the analytical validity of the test; other

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times, the amount and quality of clinical data are quite variable, ranging from results of ≥1 small retrospective studies without controls to results of prospective, randomized, controlled studies. Even among the latter, the developer may conduct without oversight by an independent agency, such as the FDA.

This situation (1) raises concern that study results are not independent of the developer's business interests and, as one might expect, (2) leads to controversy about whether the data are compelling—or not.[9-12]

What is a critical difference between PG test results and results of most laboratory tests?

PG tests are, as noted, *trait* rather than *state* characteristics. That means that the results do not change except for a phenomenon known as *phenoconversion*, discussed below. (Of course, advances in gene therapy might make it possible someday to change a person's genetic makeup and for mitochondrial genes that is perhaps already possible.)

For this reason, PG test results should not get buried in the medical record, as might happen with, say, a patient's serum potassium level at a given point in time. Instead, PG test results need to be carried forward continuously. Results also should be given to the patient as part of his (her) personal health record and to all other health care providers that the patient is seeing or will see in the future. Each health care provider who obtains PG test results should consider sending them to all current clinicians providing care for the patient at the same time as they are.

Is your functional status at a given moment the same as your genetic status?

No. There is a phenomenon known as phenoconversion in which a person's current functional status may be different from what would be expected based on their genetic status.

CYP2D6 functional status is susceptible to phenoconversion as follows: Administering fluoxetine and paroxetine, for example, at 20 or 40 mg/d converts 66% and 95%, respectively, of patients who are CYP2D6 extensive (ie, normal) metabolizers into phenocopies of people who, genetically, lack the ability to metabolize drugs via CYP2D6 (ie, genotypic CYP2D6 PM). Based on a recent study of 900 subjects in routine clinical care who were taking an antidepressant, 4% of the general U.S. population are *genetically* CYP2D6 PM; an additional 24% are *phenotypically* CYP2D6 PM because of concomitant administration of a CYP2D6 substantial inhibitor, such as bupropion, fluoxetine, paroxetine, or terbenafine.[13]

That is the reason a provider needs to know what drugs a patient is taking concomitantly—to consider the possibility of phenoconversion and, when necessary, to dose accordingly.

What does the future hold?

Development of tests for use in psychiatric practice is likely to grow substantially, for at least 2 reasons:

• There is a huge unmet need for clinically meaningful testing in providing care and, therefore, a tremendous business opportunity

• Knowledge in psychiatry is growing exponentially; with that knowledge comes the ability to develop new tests.

A recent example comes from a research group that devised a test that could predict suicidality.[14] Time will tell whether this test or a derivative of it enters practice. Nevertheless, it is a harbinger of the likely dramatic changes in the landscape of clinical medicine particularly as it applies to psychiatry.

Given this developments, the microsyndromic approach in DSM-5 will be replaced by a new diagnostic schema

that breaks down existing heterogenous syndromic diagnoses into pathophysiologically and etiologically meaningful entities using insights gained from genetic and biomarker data as well as functional brain imaging. Theoretically, those insights will lead to new modalities of treatment, including somatic treatments that target novel mechanisms of action, coupled to more effective psychosocial therapies—with both therapies guided by diagnostic tests to monitor response to specific treatment interventions.

During this transition from the past to the future, answers to the questions I've posed here about laboratory testing in psychiatry will, I hope, help the practitioner understand, evaluate, and incorporate these changes readily into practice.

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