Current PSYCHIATRY

Out of the pipeline

Pharmacogenomic DNA chip

Test anticipates adverse response to medication

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Genotyping for cytochrome (CYP) P-450 gene variations can identify patients who will not benefit from, or may react badly to, some psychotropics.[1] Psychiatrists can then more accurately tailor initial dosages to improve response and prevent adverse reactions.

An FDA-approved pharmacogenomic diagnostic DNA chip is expected to be available to clinical laboratories this month (*Table 1*). The chip provides an accurate genotype for two drug-metabolizing enzymes—2D6 and 2C19.

GENOTYPING'S ROLE IN PSYCHIATRY

CYP 2D6 and 2C19 enzymes help metabolize many commonly prescribed psychotropics, including:

- fluoxetine, paroxetine, and venlafaxine, which are among the psychotropics primarily metabolized by the cytochrome P-450 2D6 enzyme (*Table 2, page 71*).
- amitriptyline and citalopram, which are among the psychotropics metabolized in part by 2C19 (*Table 3, page 72*).

Table 1

Pharmacogenomic DNA chip: Fast facts

Brand name:
AmpliChip CYP 450 Test

FDA-approved indication:
Genotyping patients

Manufacturer:
Roche Diagnostics

Estimated availability:
July 2005

Recommended use:
Determining cytochrome P-450 2D6 and 2C19 gene variations in patients before prescribing a psychotropic metabolized through these pathways.

Laboratories that process AmpliChip results:
Labcore, Mayo Medical Laboratories, Quest Diagnostics

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Table 2

Evidence suggests these drugs are predominantly metabolized by the 2D6 enzyme*

Antidepressants	Antipsychotics	Stimulants
Desipramine	Fluphenazine	Atomoxetine
Fluoxetine	Perphenazine	
Nortriptyline	Risperidone	
Paroxetine	Thioridazine	
Venlafaxine		

*Use caution when prescribing these agents to patients who are poor 2D6 metabolizers.

The chip can identify patients who are genetically predisposed to abnormal metabolism of 2D6 and 2C19 substrates. This information can help psychiatrists improve response for ultrarapid metabolizers and minimize adverse effects experienced by poor metabolizers of these substrates.

For example, if the patient is an ultrarapid metabolizer of 2D6 and/or 2C19 substrates, the psychiatrist can:

- exceed the recommended dosage to reach adequate serum levels
- or choose an antidepressant not primarily metabolized by either enzyme.

For a poor metabolizer of 2D6 and/or 2C19 substrates, the psychiatrist can:

- choose an antidepressant metabolized by a different enzyme
- or prescribe 2D6 and 2C19 substrates at very low dosages.

For example, some poor metabolizers of 2D6 substrates have been successfully treated with fluoxetine, 2 to 5 mg/d.[2,3] This approach can help avoid side effects and potentially save the patient money. To prevent prescription errors, make sure the pharmacist understands your rationale for lower-than-recommended dosages.

continued

Table 3

Evidence suggests these drugs are predominantly metabolized by the 2C19 enzyme*

Antidepressants	
Diazepam	Citalopram
Clomipramine	Escitalopram
Imipramine	Sertraline
Benzodiazepines	
Amitriptyline	

*Use caution when prescribing these agents to patients who are poor 2C19 metabolizers.

Patients who are poor metabolizers of 2C19 and extensive metabolizers of 2D6 substrates can probably tolerate citalopram and amitriptyline dosages at the low end of the therapeutic range. Watch for high serum levels of either or both drugs if both enzyme systems are inactive.

PHARMACOGENOMIC CHIP'S ACCURACY

The 2D6 gene has more than 100 variations, many of which are very rare mutations. The pharmacogenomic DNA chip can detect 27 of these variants, allowing the chip to accurately genotype most patients. By contrast, early 2D6 genotyping techniques identified only four or five variants, resulting in too many false negatives for clinical use.[4]

The chip also can identify the normal form of the 2C19 gene and two of its variants. Both variants produce an inactive 2C19 enzyme form that is ineffective in metabolizing 2C19 substrates.

CLINICAL USE

When should a psychiatrist obtain 2D6 and 2C19 genotypes?

First, understand that the pharmacogenomic chip does not predict which medications will produce a therapeutic response. Gene chips that predict response are in development but probably will not be available before 2008.

The chip, however, can identify the relatively few ultrarapid metabolizers who will not benefit from 2D6 or 2C19 substrate medications at normal dosages, as well as "poor metabolizers" of these substrates.[1] The approximately 1% of whites in the United States who have ≥ 3 copies of the 2D6 gene metabolize 2D6 substrates very rapidly and will not respond to recommended dosages. About 10% of whites in the United States metabolize 2D6 or 2C19 substrates poorly and face increased risk of adverse reactions from these medications.

There is some evidence that the prevalence of these genetic variations differ among ethnicities. Approximately 15% of Saudi Arabians and 20% of Ethiopians are ultrarapid metabolizers of 2D6 and 2C19 substrates.[5,6]

The most common 2D6 poor metabolizer allele (*4) has been found in 12% to 21% of whites, whereas 23% to 32% of Asians and 13% of whites have the most common 2C19 poor metabolizer allele (*2).[6-10] Prevalence of poor 2D6 and/or 2C19 metabolism among African Americans, Hispanics, and Native Americans has not been established.

> The chip can detect 27 2D6 gene variants, allowing it to accurately genotype most patients

CLINICAL PRACTICALITY

Clinicians' unfamiliarity with genotyping and cost concerns pose potential barriers to the test's use.

Clinician knowledge. Pharmacogenomic 2D6 and 2C19 tests will soon be offered nationwide at reference laboratories such as Quest Diagnostics, Labcore, and Mayo Medical Laboratories. The psychiatrist can call the lab for instructions, then send a blood sample and receive results by mail within 2 to 3 days.

While I believe the test's usefulness will soon

be widely understood, courses are available to help clinicians learn about genetic testing. Mayo Clinic College of Medicine (http://www.mayo.edu/cme/genomics.html) offers an annual week-long CME course in August. The American Psychiatric Association, as part of its May 2006 annual meeting, will offer a similar half-day course led by Mayo Clinic psychiatrists.

Cost. The exact cost of using the pharmacogenomic chip varies, as each laboratory sets fees for genotyping. Even so, genotyping could offer enormous cost savings by preventing failed medication trials and reducing the need for more-intensive psychiatric care. Furthermore, many insurance companies cover genotype testing.

Related resources

- Pharmacogenomic diagnostic DNA chip product information. www.roche-diagnostics.com/products_services/amplichip_cyp450.html.
- Kirchheiner J, Borsen K, Dahl ML, et al. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. *Acta Psychiatr Scand* 2001;103(3):173-92.

DRUG BRAND NAMES

Amitriptyline • Elavil
Atomoxetine • Strattera
Citalopram • Celexa
Clomipramine • Anafranil
Desipramine • Norpramin
Diazepam • Valium
Escitalopram • Lexapro
Fluoxetine • Prozac
Fluphenazine • Prolixin
Nortriptyline • Pamelor
Paroxetine • Paxil
Perphenazine • Trilafon
Risperidone • Risperdal

DISCLOSURE

Dr. Mrazek is a consultant to Predix Pharmaceuticals.

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10. Sachse C, Brockmoller J, Bauer S, Roots I. Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. *Am J Hum Genet* 1997;60:284-95.

Bottom Line

A pharmacogenomic DNA chip can help identify patients who might not respond, or may respond badly, to CYP-450 2D6 and 2C19 substrates. This and other anticipated genomic advances may soon help psychiatrists predict response to medications and improve outcomes.