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. 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

<table>
<thead>
<tr>
<th>Brand name:</th>
<th>AmpliChip CYP 450 Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved indication:</td>
<td>Genotyping patients</td>
</tr>
<tr>
<td>Manufacturer:</td>
<td>Roche Diagnostics</td>
</tr>
<tr>
<td>Estimated availability:</td>
<td>July 2005</td>
</tr>
<tr>
<td>Recommended use:</td>
<td>Determining cytochrome P-450 2D6 and 2C19 gene variations in patients before prescribing a psychotropic metabolized through these pathways.</td>
</tr>
<tr>
<td>Laboratories that process AmpliChip results:</td>
<td>Labcore, Mayo Medical Laboratories, Quest Diagnostics</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Antipsychotics</th>
<th>Stimulants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine</td>
<td>Fluphenazine</td>
<td>Atomoxetine</td>
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<tr>
<td>Fluoxetine</td>
<td>Perphenazine</td>
<td></td>
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<tr>
<td>Nortriptyline</td>
<td>Risperidone</td>
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<tr>
<td>Paroxetine</td>
<td>Thioridazine</td>
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<tr>
<td>Venlafaxine</td>
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</tbody>
</table>

*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.

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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. 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. 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). Prevalence of poor 2D6 and/or 2C19 metabolism among African Americans, Hispanics, and Native Americans has not been established.

**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.

**References**


**Related resources**


**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.

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.