Genotyping The Patient
Requiring Mental Health Medications:
When Does It Make Sense?

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Storrs, CT
I have NO actual or potential conflicts of interest in relation to this educational presentation.
No Off-Label Discussions
Learning Objectives

• Discuss genomic variability in terms of psychotropic drug outcomes;
• Describe clinical pharmacogenomic tests that practitioners can use in support of clinical care;
• Understand the limitations of clinical pharmacogenomic testing as applied to the use of psychotropic medications.
Psychotropic Drug Outcome Variability
Dose–Effect Relationship in Pharmacology

Drug dose → Biologic fluid concentration → Effect site concentration → Pharmacologic effect

Pharmacokinetic variability:
- Bioavailability (F)
- Metabolism
- Protein binding/protein status
- Sub-optimal adherence
- Efflux transport

Pharmacodynamic variability:
- Low “F” drugs
- Long $T_{1/2}$ drugs
- Metabolic routes
- Efflux substrates

Pharmacokinetic variability:
- Target site [ ]
- Affinity
- Dissociation
- Other drugs
The US Food and Drug Administration (FDA) today announced the approval of the cobas EGFR Mutation Test, a companion diagnostic for the cancer drug erlotinib (Tarceva). This is the first FDA-approved companion diagnostic that can detect epidermal growth factor receptor (EGFR) gene mutations, which are present in approximately 10% of non-small cell lung cancers (NSCLCs).

The approval of this test comes at the same time as an expanded indication for erlotinib. The FDA has also announced a labeling change for erlotinib, and the drug is now indicated for first-line use in patients with metastasized NSCLC that tests positive for EGFR mutations. Until now, the official indication was second- or third-line use in advanced NSCLC.

"The approval of the cobas EGFR Mutation Test will allow physicians to identify non-small cell lung cancer patients who are candidates for receiving Tarceva as first-line therapy," said Alberto Gutierrez, PhD, director of the Office of In Vitro Diagnostics and Radiological Health in the FDA’s Center for Devices and Radiological Health, in a statement. "Companion diagnostics play an important role in determining which therapies are the safest and most effective for a particular patient."

Most Popular Articles
According to PSYCHIATRISTS

1. NIMH, APA Clash Over Upcoming DSM-5
2. Non-Steroidal Anti-Inflammatory Drugs May Reduce Schizophrenia Symptoms: Safety in the Short Term When Added to Antipsychotics
3. Amphetamine-Induced Psychosis
4. Antidepressants Linked to Doubling of Clostridium difficile Risk
5. Pharmacogenomics of Bipolar Disorder

BECOME THE LEADER YOU’D ACTUALLY WANT TO WORK FOR
Table 1: Three Ranges of Expected Maintenance COUMADIN Daily Doses Based on CYP2C9 and VKORC1 Genotypes

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/*1</td>
</tr>
<tr>
<td>GG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AA</td>
<td>3-4 mg</td>
</tr>
</tbody>
</table>

*Ranges are derived from multiple published clinical studies. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.*

http://packageinserts.bms.com/pi/pi_coumadin.pdf accessed on 22 May 2013
PLAVIX (clopidogrel bisulfate) tablets
Initial U.S. Approval: 1997

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)

- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)

- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)

- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)
Pgp export pump

Distribution

Absorption

Metabolism

[ ] @ target site

Elimination
Table 1  Validated ABCB1 gene single nucleotide polymorphisms and their associations with major depressive disorder

<table>
<thead>
<tr>
<th>SNP_ID</th>
<th>Chromosome</th>
<th>Allele</th>
<th>Role</th>
<th>MAF</th>
<th>N</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1882478</td>
<td>B6D7954</td>
<td>T/C</td>
<td>Intron 27</td>
<td>0.47</td>
<td>100</td>
<td>0.062</td>
<td>0.28</td>
</tr>
<tr>
<td>rs2236048</td>
<td>B6D76447</td>
<td>T/C</td>
<td>Intron (boundary) 27</td>
<td>0.42</td>
<td>100</td>
<td>0.037</td>
<td>0.37</td>
</tr>
<tr>
<td>rs2236047</td>
<td>B6D76468</td>
<td>T/G</td>
<td>Intron (boundary) 27</td>
<td>0.36</td>
<td>100</td>
<td>0.74</td>
<td>0.68</td>
</tr>
<tr>
<td>rs1048440 (C3428G)</td>
<td>B6D79581</td>
<td>G/T</td>
<td>Coding exon 27</td>
<td>0.42</td>
<td>95</td>
<td>0.057</td>
<td>0.27</td>
</tr>
<tr>
<td>rs60494489</td>
<td>B6D79750</td>
<td>G/T</td>
<td>Intron 26</td>
<td>0.42</td>
<td>91</td>
<td>0.19</td>
<td>0.20</td>
</tr>
<tr>
<td>rs10234441</td>
<td>B7002928</td>
<td>A/T</td>
<td>Intron 21</td>
<td>0.48</td>
<td>99</td>
<td>0.20</td>
<td>0.56</td>
</tr>
<tr>
<td>rs7658103</td>
<td>B7003903</td>
<td>G/A</td>
<td>Intron 20</td>
<td>0.18</td>
<td>100</td>
<td>0.52</td>
<td>0.16</td>
</tr>
<tr>
<td>rs1822242</td>
<td>B7011302</td>
<td>A/T</td>
<td>Intron (boundary) 17</td>
<td>0.26</td>
<td>98</td>
<td>0.0028</td>
<td>0.39</td>
</tr>
<tr>
<td>rs1233264</td>
<td>B7012302</td>
<td>A/G</td>
<td>Intron (boundary) 17</td>
<td>0.38</td>
<td>100</td>
<td>0.011</td>
<td>0.041</td>
</tr>
<tr>
<td>rs1128503 (C1238T)</td>
<td>B6D717957</td>
<td>T/C</td>
<td>Coding exon 13</td>
<td>0.41</td>
<td>100</td>
<td>0.015</td>
<td>0.020</td>
</tr>
<tr>
<td>rs2530181</td>
<td>B6D37301</td>
<td>A/G</td>
<td>Intron 5</td>
<td>0.17</td>
<td>98</td>
<td>0.97</td>
<td>0.30</td>
</tr>
<tr>
<td>rs2340184</td>
<td>B7037348</td>
<td>T/G</td>
<td>Intron (boundary) 6</td>
<td>0.04</td>
<td>99</td>
<td>0.37</td>
<td>0.81</td>
</tr>
<tr>
<td>rs10258836</td>
<td>B7043839</td>
<td>G/C</td>
<td>Intron 5</td>
<td>0.14</td>
<td>100</td>
<td>0.61</td>
<td>0.06</td>
</tr>
<tr>
<td>rs1080891</td>
<td>B7043415</td>
<td>T/A</td>
<td>Intron 5</td>
<td>0.06</td>
<td>100</td>
<td>0.39</td>
<td>0.80</td>
</tr>
<tr>
<td>rs1202184</td>
<td>B70561397</td>
<td>A/G</td>
<td>Intron 5</td>
<td>0.33</td>
<td>100</td>
<td>0.0021</td>
<td>0.0013</td>
</tr>
<tr>
<td>rs1976843</td>
<td>B7056822</td>
<td>C/T</td>
<td>Intron 4</td>
<td>0.26</td>
<td>100</td>
<td>0.11</td>
<td>0.56</td>
</tr>
<tr>
<td>rs2189524</td>
<td>B7063971</td>
<td>A/G</td>
<td>Intron (boundary) 1</td>
<td>0.07</td>
<td>100</td>
<td>0.34</td>
<td>0.01</td>
</tr>
<tr>
<td>rs26381796</td>
<td>B7069847</td>
<td>T/C</td>
<td>Intron 1</td>
<td>0.05</td>
<td>100</td>
<td>0.35</td>
<td>0.80</td>
</tr>
<tr>
<td>rs4140732</td>
<td>B7071985</td>
<td>A/G</td>
<td>Intron 1</td>
<td>0.12</td>
<td>100</td>
<td>0.008</td>
<td>0.44</td>
</tr>
<tr>
<td>rs1976890</td>
<td>B7066677</td>
<td>T/C</td>
<td>Intron 1</td>
<td>0.20</td>
<td>100</td>
<td>0.33</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Bold text: P<0.05.

ABCB1, ATP-binding cassette, sub-family B (NDF/TPA), member 1; HAM-A, Hamilton Depression Rating Scale for anxiety; HAM-D, Hamilton Depression Rating Scale for Depression; MAF, minor allele frequency; N, subject number; P, permutation bootstrap for 10,000 P values; SNP, single nucleotide polymorphism.

1According to the dbSNP database (parentheses indicate that the SNP is within an exon locus).

2Based upon NCBI Human Genome Build 35.

3The second allele is the minor allele.

4Minor allele frequency (parentheses: minor allele frequency in HapMap Chinese population, except rs26381796 which is from an Asian population).

5Hamilton Depression Rating Scale to quantify the severity of depression symptoms adjusted with HAM-A.

6Hamilton Anxiety Rating Scale to quantify the severity of anxiety symptoms adjusted with HAM-D.

7Permutation bootstrap for 10,000 P values for the SNP genotypes and adjusted with HAM-D or HAM-A association analyses.

Drug Metabolism

Drug → Metabolite #1 (CYP450*)

Metabolite #1 → Metabolite #2 (UDPG*)

*Activity modifiable by other meds, and by genetics
CYP450 Genes

<table>
<thead>
<tr>
<th>CYP450 Enzyme</th>
<th>Chromosome</th>
<th>Alleles*</th>
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</thead>
<tbody>
<tr>
<td>1A2</td>
<td>15</td>
<td>41</td>
</tr>
<tr>
<td>2B6</td>
<td>19</td>
<td>62</td>
</tr>
<tr>
<td>2C9</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>2C19</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>2D6</td>
<td>22</td>
<td>142</td>
</tr>
<tr>
<td>2E1</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>3A4</td>
<td>7</td>
<td>42</td>
</tr>
</tbody>
</table>

CYP2D6 Allele Frequency

Drug Action
Serotonin Transporter Alleles

Treatment Outcomes

• Dependent upon:
  - Proper dx, proper tx selected
  - Patient adherence to tx
  - Dose/duration of tx
  - Environmental stress
  - Pharmacokinetics & pharmacodynamics
    ‣ Genetics
    ‣ Other medications
2

Clinical PGx Tests
## Psychotropics w/ PGx Labeling

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Therapeutic Area</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>Depression/Anxiety</td>
<td>Citalopram, diazepam</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>ADHD</td>
<td>Atomoxetine</td>
</tr>
<tr>
<td></td>
<td>Depression/Anxiety</td>
<td>Aripiprazole, citalopram, clomipramine, desipramine, doxepin, fluoxetine,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fluvoxamine, nefazodone, nortriptyline, paroxetine, venlafaxine</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous</td>
<td>Codeine, fluoxetine/olanzapine, iloperidone, modafinil, perphenazine,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>risperidone</td>
</tr>
<tr>
<td>HLA-B*1502</td>
<td>Bipolar disorder</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>UCD</td>
<td>Bipolar disorder</td>
<td>Valproic acid</td>
</tr>
</tbody>
</table>

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm accessed on 15 May 2013
Celexa®

**QT-Prolongation and Torsade de Pointes**

Citalopram causes dose-dependent QTc prolongation, an ECG abnormality that has been associated with Torsade de Pointes (TdP), ventricular tachycardia, and sudden death, all of which have been observed in postmarketing reports for citalopram.

The citalopram dose should be limited in certain populations. The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers or those patients who may be taking concomitant cimetidine or another CYP2C19 inhibitor, since higher citalopram exposures would be expected. The maximum dose should also be limited to 20 mg/day in patients with hepatic impairment and in patients who are greater than 60 years of age because of expected higher exposures.
2.4 Dosing in Specific Populations

Dosing adjustment for hepatically impaired patients — For those ADHD patients who have hepatic insufficiency (HI), dosage adjustment is recommended as follows: For patients with moderate HI (Child-Pugh Class B), initial and target doses should be reduced to 50% of the normal dose (for patients without HI). For patients with severe HI (Child-Pugh Class C), initial dose and target doses should be reduced to 25% of normal [see Use in Specific Populations (8.6)].

Dosing adjustment for use with a strong CYP2D6 inhibitor or in patients who are known to be CYP2D6 PMs — In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, or in patients who are known to be CYP2D6 PMs, STRATTERA should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

In children and adolescents over 70 kg body weight and adults administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, STRATTERA should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.
Figure 1  Codeine metabolism pathway.
Table 1  Assignment of likely codeine metabolism phenotypes based on CYP2D6 diplotype

<table>
<thead>
<tr>
<th>Likely phenotype</th>
<th>Activity score</th>
<th>Genotypes</th>
<th>Examples of diplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>&gt;2.0</td>
<td></td>
<td>*1/*1XN, *1/*2xN</td>
</tr>
<tr>
<td>Extensive metabolizer (77–92% of patients)</td>
<td>1.0–2.0b</td>
<td>An individual carrying two alleles encoding full or reduced function or one full function allele together with either one nonfunctional or one reduced-function allele</td>
<td>*1/*71, *1/*72, *2/*72, *1/*41, *1/*4, *2/*5, *10/*10</td>
</tr>
<tr>
<td>Intermediate metabolizer (2–11% of patients)</td>
<td>0.5b</td>
<td>An individual carrying one reduced and one nonfunctional allele</td>
<td>*4/*10, *5/*41</td>
</tr>
<tr>
<td>Poor metabolizer (5–10% of patients)</td>
<td>0</td>
<td>An individual carrying no functional alleles</td>
<td>*4/*4, *4/*5, *5/*5, *4/*6</td>
</tr>
</tbody>
</table>

The frequency estimates are based on data from Caucasians and may differ substantially for other ethnicities. See Supplementary Data online for estimates of phenotype frequencies among different ethnic/geographic groups. Note that some investigators define patients with an activity score of 0.5 and 1.0 as intermediate metabolizers and define patients with an activity score of 1.5 and 2.0 as extensive metabolizers. Classifying patients with an activity score of 1.0 as extensive metabolizers in this guideline is based on data specific for formation of morphine from codeine in these patients.

Table 2  Codeine therapy recommendations based on CYP2D6 phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for codeine metabolism</th>
<th>Recommendations for codeine therapy</th>
<th>Classification of recommendation for codeine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>Increased formation of morphine following codeine administration, leading to higher risk of toxicity</td>
<td>Avoid codeine use due to potential for toxicity. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol.</td>
<td>Strong</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Normal morphine formation</td>
<td>15–60 mg every 4 h as needed for pain (label recommendation)</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Reduced morphine formation</td>
<td>Begin with 15–60 mg every 4 h as needed for pain. If no response, consider alternative analgesics such as morphine or a nonopioid. Monitor tramadol use for response.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief</td>
<td>Avoid codeine use due to lack of efficacy. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol.</td>
<td>Strong</td>
</tr>
</tbody>
</table>

*Rating scheme is described in Supplementary Data online. Although detailed recommendations for using CYP2D6 phenotype in tramadol therapy are beyond the scope of this guideline, there is strong evidence for decreased efficacy of tramadol in poor metabolizers and a single case report of toxicity in an ultrarapid metabolizer with renal impairment following tramadol postsurgery. Use of other analgesics in CYP2D6 poor metabolizers and ultrarapid metabolizers may therefore be preferable.*
Ultra-Rapid Metabolizer

Increased risk of not achieving adequate concentrations of drug with conventional dosing…
increased risk of poor therapeutic response

Drug Concentration Using Conventional Dosing

Adverse
Therapeutic
Ineffective

Time

CF Caley, Pharm.D., BCPP
Poor Metabolizer

Increased risk of achieving excessive concentrations of drug with conventional dosing…
increased risk of poor tolerability d/t adverse effects

Drug Concentration
Using Conventional
Dosing

Time

Adverse

Therapeutic

Ineffective

CF Caley, Pharm.D., BCPP
<table>
<thead>
<tr>
<th>Lab</th>
<th>Web</th>
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<tbody>
<tr>
<td>PGXL Laboratories</td>
<td>pgxlab.com</td>
<td>Louisville, KY</td>
</tr>
<tr>
<td>Millenium Laboratories</td>
<td>milleniumlabs.com</td>
<td>San Diego, CA</td>
</tr>
<tr>
<td>Genelex</td>
<td>vouscript.com</td>
<td>Seattle, WA</td>
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<tr>
<td>Genesys Diagnostics</td>
<td>gdilabs.com</td>
<td>East Lyme, CT</td>
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<tr>
<td>ARUP Laboratories</td>
<td>aruplabs.com</td>
<td>Salt Lake City, UT</td>
</tr>
<tr>
<td>Genomas</td>
<td>genomas.net</td>
<td>Hartford, CT</td>
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<td>Genova Diagnostics</td>
<td>gdx.net</td>
<td>Duluth, GA</td>
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<td>Mayo Medical Labs</td>
<td>mayomedicallaboratories.com</td>
<td>Rochester, MN</td>
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<tr>
<td>AssureRx</td>
<td>assurerxhealth.com</td>
<td>Mason, OH</td>
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</tbody>
</table>
**HILOmet 2D6**

**CYTOCHROME P450 DNA TYPING REPORT, GENE CYP2D6**

<table>
<thead>
<tr>
<th>ALLELES</th>
<th>CARRIER STATUS</th>
<th>METABOLIZER STATUS</th>
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</thead>
<tbody>
<tr>
<td><strong>WT</strong></td>
<td>□ Gene Duplication</td>
<td>□ Ultra-rapid</td>
</tr>
<tr>
<td>*5</td>
<td>□ Normal</td>
<td>□ Functional</td>
</tr>
<tr>
<td>*17</td>
<td>□ Carrier</td>
<td>□ Deficient</td>
</tr>
<tr>
<td>*6</td>
<td>□ Double</td>
<td>□ Null</td>
</tr>
<tr>
<td>*4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*3</td>
<td></td>
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<tr>
<td>*9</td>
<td></td>
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<tr>
<td>*10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duplication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other:</td>
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<td></td>
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</tbody>
</table>

- Specimen did not meet LPH acceptability

Comments/recommendations:

Please refer to the LPH website at [www.genomas.net/lph](http://www.genomas.net/lph) for additional clinical and scientific background information.

Signed: ____________________________  
Gualberto Ruaño, M.D., Ph.D.  
Laboratory Director

1. The HILOmet System should be used only in conjunction with clinical presentation and other diagnostic data when making therapy decisions. A Patient's response to drug therapy depends on multiple non-genetic factors, including patient compliance with drug regimen, interactions with other medications, and diet.

2. The HILOmet System, including DNA extraction and DNA typing of cytochrome p450 genes, was performed by the Laboratory of Personalized Health (LPH) under its license from the CT Department of Public Health (license CL-0644) and certification with the Centers for Medicare and Medicaid (ID# 07D1036625) under the CLIA (Clinical Laboratory Improvement Amendments). The HILOmet test has not been cleared or approved by the U.S. Food and Drug Administration (FDA); FDA approval or clearance is not required for the HILOmet System.
Pharmacogenomics

Psychiatry

We currently offer the following pharmacogenomic tests for psychiatry:

Antidepressants and/or Antipsychotics

- Serotonin Transporter Genotype, Blood
  Comprehensive assay to assist in determining response to SSRIs and optimize antidepressant therapy.
- Catechol-O-Methyltransferase Genotype
  Inhibitor of L-Dopa metabolism and early identification of patients who may show cognitive improvement with treatment of schizophrenia (*2/*2 genotype).
- Cytochrome P450 1A2 Genotype: Blood | Saliva
  Optimization of antipsidressant therapy.
- Cytochrome P450 2C19 Genotype by Sequence Analysis: Blood | Saliva
  Optimization of psychiatric medications. Also useful for clozapine.
- Cytochrome P450 2C9 Genotype by Sequence Analysis: Blood | Saliva
  Optimization of antidepressants. Also useful for warfarin resistance.
- Cytochrome P450 2D6 Genotype
  Optimization of psychiatric medications. Also useful for Tamsulosin.
- Dopamine Receptor D3 Genotype (DAR3)
  Aid in determining risk of antipsychotic induced tardive dyskinesia.
- Dopamine Receptor D4 Genotype (DAR4)
  Monitoring response to methylenidate in Attention Deficit Hyperactivity Disorder (ADHD) patients.
- Serotonin Receptor Genotype (HTR2A and HTR2C)
  Monitoring response to antidepressants and some antipsychotics.
- Opioid Receptor, Mu 1 (OPRM1) Genotype for Naltrexone Efficacy
  Prediction of response of alcoholism to naltrexone.

AssureRx Health Launches Personalized Medicine Test for ADHD

Mason, OH - May 7, 2012 - AssureRx Health, Inc. today announced it has launched a personalized medicine test for the growing number of children and adults diagnosed with attention deficit hyperactivity disorder (ADHD). The new pharmacogenomic test can assist clinicians with important medication decisions that result from genomic differences in how individual patients tolerate ADHD medications.

GeneSightRx ADHD analyzes variations in three genes that influence how a patient might metabolize certain medications used to treat ADHD in children and adults. Understanding a patient’s unique genomic profile may help a clinician individualize a patient’s medication selection and avoid side effects that often occur with these medications. The test provides objective, evidence-based information for clinicians to personalize medication selection for each patient.

The GeneSightRx ADHD analysis is based on pharmacogenomics, FDA-approved manufacturer’s drug labels, published peer reviewed research, and proven pharmacology. The new ADHD test adds to the company’s treatment decision support products that include GeneSightRx Psychotropic, a psychiatric pharmacogenomic product that tests important genomic variants affecting metabolism to psychiatric medications for individual patients.

ADHD diagnoses increased 66 percent from 6.2 million in 2000 to 10.4 million in 2010, according to a study published in the March/April 2012 issue of Academic Pediatrics. ADHD is the most common childhood disorder and can continue into adulthood. Symptoms of ADHD include an inability to stay focused or pay attention, difficulty controlling behavior, and hyperactivity.

“ADHD is a neurobehavioral disorder affecting millions of children and adults. With the introduction of GeneSightRx ADHD, clinicians now have an objective, evidence-based tool for individualizing ADHD medications,” said James S. Burns, president and CEO of AssureRx Health. “Our goal is to build a portfolio of innovative pharmacogenomic and other treatment decision support products to help physicians individualize the treatment of patients with neuropsychiatric and other disorders.”

When a clinician orders the test, a DNA sample is taken from the patient with a simple, non-invasive
**GeneSightRx® ADHD Results**

**Patient, Sample**

DOB: 11/14/1984

**Reference:** 1458COP  
**Clinician:** Sample Clinician

**Order Number:** 9209  
**Report Date:** 4/23/2012

**Patient Genotypes and Phenotypes**

**CYP2D6**  
**Poor Metabolizer**  
*4/*4

**Comment:** This genotype is associated with a poor metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal genotype.

**COMT**  
**High Activity**  
VAL/VAL

**ADRA2A**  
**Improved Response**  
C/G

**Drugs are reported in alphabetical order. This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drugs being considered and make treatment decisions based on the patient's individual needs and the characteristics of the drug prescribed.**

[1]: CYP2D6 genotype indicates that blood levels may be increased for this drug.  
[2]: CYP2D6 genotype indicates that blood levels may be decreased for this drug.  
[3]: COMT genotype is associated with reduced therapeutic response to this drug.  
[4]: ADRA2A genotype is associated with improved response to this drug.  
[5]: CYP2D6 genotype indicates that this patient may experience increased side-effects, but also increased efficacy.
Some ADHD medications are metabolized by the CYP2D6 enzyme. Concomitant use of these medications with substances known to inhibit CYP2D6 enzyme activity may result in increased levels of the ADHD medication.

### ADHD Medications Metabolized by the CYP2D6 enzyme

- amphetamine salts (Adderall®)
- dextroamphetamine (Dexedrine®)
- lisdexamfetamine (Vyvanse®)
- atomoxetine (Strattera®)

### Known inhibitors of CYP2D6 enzyme activity

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antianginal</td>
<td>nicardipine, ranolazine</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
<td>amiodarone, quinidine</td>
</tr>
<tr>
<td>Antibacterial</td>
<td>amoxicillin, clindamycin, doxycycline, imipenem, minocycline, tetracycline, trimethoprim</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>darifenacin, glycopyrrolate, neostigmine, propantheline, pyridostigmine</td>
</tr>
<tr>
<td>Antifungal</td>
<td>ketaconazole, miconazole, terbinafine</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>diphenhydramine, doxepine, loratadine, promethazine, pyrilamine</td>
</tr>
<tr>
<td>Antimicrobial</td>
<td>chloramphenicol, clindamycin, erythromycin, fusidic acid, gentamicin</td>
</tr>
<tr>
<td>Antineoplastic</td>
<td>imatinib, daunorubicin, doxorubicin, oxaliplatin</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>chlorpromazine, clozapine, haloperidol, olanzapine, quetiapine</td>
</tr>
<tr>
<td>Antiretroviral</td>
<td>delavirdine, efavirenz, nelfinavir, ritonavir, saquinavir, tenofovir</td>
</tr>
<tr>
<td>Antithyroid</td>
<td>methimazole, lithium, propylthiouracil</td>
</tr>
<tr>
<td>Antiulcer</td>
<td>cimetidine, ranitidine</td>
</tr>
<tr>
<td>Antiviral</td>
<td>acyclovir, famciclovir, famotidine, ganciclovir, penciclovir</td>
</tr>
<tr>
<td>Antiviral</td>
<td>zidovudine, abacavir, didanosine, emtricitabine, lamivudine, stavudine</td>
</tr>
<tr>
<td>Local Anesthetic</td>
<td>lidocaine, mepivacaine, prilocaine</td>
</tr>
<tr>
<td>Psychostimulant</td>
<td>dextroamphetamine, modafinil</td>
</tr>
</tbody>
</table>

This drug interaction information is based upon data available in scientific literature and prescribing information for the most commonly prescribed drugs. Only CYP2D6 interactions based on published data from in vivo studies showing moderate to significant induction/inhibition, as defined by the FDA, are listed. The degree of inhibition may vary. Additional interactions may exist. Please reference FDA approved drug information for additional drug interaction data.
Test Information:
The buccal swab sample was collected on 4/21/2012 and received in the laboratory on 4/22/2012. Genomic DNA was isolated and the relevant genomic regions were amplified by polymerase chain reaction (PCR). CYP2D6 was analyzed using xTAG™ kits (Luminex Molecular Diagnostics). COMT and ADRA2A were analyzed using custom xTAG™ assays. The following genetic variants may be detected in the assay: CYP2D6 *1, *2, *3A, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *41, gene duplication; COMT Val158Met; ADRA2A -1291C>G. The following rare genetic variants have not been observed by the AssureRx Health, Inc. laboratory: CYP2D6 *8, *12.

This test was developed and its performance characteristics determined by AssureRx Health, Inc. It has not been cleared or approved by the U.S. Food and Drug Administration.

These interpretations are based upon data available in scientific literature and prescribing information for the relevant drugs. Interpretations are, in some instances, based on data regarding the pharmacokinetic, pharmacodynamic and pharmacogenomic properties of a drug derived from non-clinical studies, including in-vitro and animal studies. Findings from studies performed in a non-clinical setting or clinical studies involving healthy subjects are not necessarily indicative of clinical performance in a particular patient.

This report was reviewed and verified on 4/23/2012 by:

Nina King, PhD
Laboratory Director, AssureRx Health, Inc.

Disclaimer of Liability:
The information contained in this report is provided as a service and does not constitute medical advice. At the time of report generation this information is believed to be current and is based upon published research; however, research data evolves and amendments to the prescribing information of the drugs listed will change over time. While this report is believed to be accurate and complete as of the date issued, THE DATA IS PROVIDED "AS IS", WITHOUT WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION, THE IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. As medical advice must be tailored to the specific circumstances of each case, the treating health care professional has ultimate responsibility for all treatment decisions made with regard to a patient including any made on the basis of a patient's genotype.

Genetic testing was completed by a CLIA certified and CAP accredited laboratory in the United States located at:

6030 S. Mason Montgomery Rd.
Mason, OH 45040

Customer Support:
Healthcare professionals please contact AssureRx Health at 1-866-757-9204 or support@assurerxhealth.com for assistance with this report. Please note that AssureRx Health cannot provide healthcare related answers directly to patients. Patients should direct any questions to their healthcare professional.
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Limitations
Drug Metabolism

Drug → Metabolite #1

Metabolite #1 → Metabolite #2

*CYP450* and *UDPG* activities are modifiable by other medications and genetics.
Citalopram Metabolism

MDD

Limitations

- Tendency to oversimplify drug metabolism
- Incomplete understanding of pathophysiology
- Inconsistent results for replicating genetic association between biomarkers and outcomes
  - Patient sample diagnostic heterogeneity
  - Study methodologies
    - Screening for specific polymorphisms vs. performing genome-wide association
- Key variables: treatment non-adherence; impact of environmental stress; impact of other genes
Examples