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**Using Pharmacogenetic Markers in Clinical Treatment**

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Using Pharmacogenetic Markers in Clinical Treatment: The Pros and Cons of Preemptive Genetic Testing

6 November 2013

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Participating Expert:

Ulrich Broeckel, M.D.
Medical College of Wisconsin
Milwaukee, WI

Moderator:

Sean Sanders, Ph.D.
Science/AAAS
Washington, DC

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Using Pharmacogenetic Markers in Clinical Treatment: The Pros and Cons of Preemptive Genetic Testing

Ulrich Broeckel, MD
Section of Genomic Pediatrics
Department of Pediatrics
Medical College of Wisconsin

@broeckel_lab
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PGRN
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Teri Klein
Alan Shuldiner
Julie Johnson
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Don Baker
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Kiran Bobba
Where should we start…

Genetics, genetics, genetics…

Individualized Medicine….

Technology drives research
Research drives clinical application
Research and clinical applications drive health

The New Challenge:
Implementation of genetic information into clinical practice
Concepts of PGX Genotyping

2008:

As we are moving to genome analysis, can we start implementing comprehensive analyses using well established examples?

“Walk before running”
Pharmacogenetics

**Pharmacogenetics:** Study the factors which influence the response and effectiveness related to drug treatment

Historically PGX focused on

- drug becomes active component
- drug gets inactivated/excreted
- variation in drug target
- side effects, toxicity, off target effects
Concepts of PGX Genotyping 1

Clinical PGX testing is mainly / currently

- drug driven
- candidate gene driven
- single drug – single gene
- reactive
Concepts of PGX Genotyping 2

Small set of established relevant PGX genes

Commonly tested genes are relevant to a broad spectrum of drugs

PGX testing results will retain relevance
Concepts of PGX Genotyping 3

Target area: PGX

Comprehensive genotyping platform: DMET Plus

Target patient population:

- Children with childhood cancer
- St Jude’s Children’s Research Hospital, Memphis

Pre-emptive PGX Genotyping
PG4KDS: CLINICAL IMPLEMENTATION OF PHARMACOGENETICS

Goal: migrate pharmacogenetic tests from laboratory (array-based) into routine patient care, to be available preemptively

http://www.stjude.org/pg4kds
Genotyping using Affymetrix DMET Plus Array

225 ADME genes

Analysis software for translation to standard nomenclature

- A tabular comprehensive genotyping report containing pharmacogenomic reference data on all probes
- A variant summary in similar format, where defining SNPs are systematically retrieved
- A phenotype report on a subset of higher-visibility genes
- An uncalled report detailing the missing genotypes within translated genes
DMET Plus Array: Assessment

1. Quality control
2. Determine the call rate of 1,931 SNPs in all patient samples
   - Remove SNPs with call rates < 98% (n = 171 SNPs)
3. Determine the Hardy-Weinberg equilibrium of SNPs
   - Remove SNPs that are not in equilibrium at P > 0.001 (n = 80 SNPs)
4. 1,692 DMET SNPs passed quality control
5. Match DMET SNPs with orthogonal genotype/sequencing methods
6. 259 DMET SNPs overlap with ≥1 orthogonal methods
7. Determine concordance between the methods
8. Resolve any discrepancies with additional genotyping/sequencing available

Genotyping using Affymetrix DMET Plus Array

Table 1  Concordance between DMET genotyping and orthogonal methods

<table>
<thead>
<tr>
<th>Genotype platform</th>
<th>No. of SNPs that overlapped with those typed on DMET Plus</th>
<th>No. of samples typed by both methods</th>
<th>Total no. of SNP-patient samples typed</th>
<th>No. of discordant genotypes</th>
<th>% Concordant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beckman Coulter GenomeLab SNPstream, DNA PrintGenomics</td>
<td>7</td>
<td>22–34</td>
<td>192</td>
<td>5</td>
<td>97.4</td>
</tr>
<tr>
<td>GeneChip Human Mapping Array (SNP6/500K), Affymetrix</td>
<td>167</td>
<td>88</td>
<td>14,637</td>
<td>21</td>
<td>99.9</td>
</tr>
<tr>
<td>Prometheus TPMT Genetics</td>
<td>3</td>
<td>215</td>
<td>644</td>
<td>2</td>
<td>99.7</td>
</tr>
<tr>
<td>Sanger sequencing, Affymetrix</td>
<td>26</td>
<td>67</td>
<td>1,736</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Custom-designed GoldenGate array, Illumina</td>
<td>78</td>
<td>32</td>
<td>2,492</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>iplex Gold MassARRAY platform, Sequenom</td>
<td>8</td>
<td>31</td>
<td>241</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

DMET, Drug Metabolizing Enzymes and Transporters Plus array; SNP, single-nucleotide polymorphism.

DMET Plus Array: Assessment

<table>
<thead>
<tr>
<th>Discordant patient ID</th>
<th>rsID</th>
<th>Gene</th>
<th>DMET genotype</th>
<th>SNPstream genotype</th>
<th>SNP6/500K genotype</th>
<th>GoldenGate genotype</th>
<th>Concordant methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rs1800566</td>
<td>NQO1</td>
<td>C/C</td>
<td>C/T</td>
<td>C/C</td>
<td>C/C</td>
<td>DMET, SNP6/500K, and GoldenGate</td>
</tr>
<tr>
<td>2</td>
<td>rs1800566</td>
<td>NQO1</td>
<td>C/T</td>
<td>T/T</td>
<td>C/T</td>
<td>C/T</td>
<td>DMET, SNP6/500K, and GoldenGate</td>
</tr>
<tr>
<td>2</td>
<td>rs1045642</td>
<td>ABCB1</td>
<td>C/C</td>
<td>C/T</td>
<td>C/C</td>
<td>None available</td>
<td>DMET and SNP6/500K</td>
</tr>
<tr>
<td>2</td>
<td>rs776746</td>
<td>CYP3A5</td>
<td>A/G</td>
<td>G/G</td>
<td>A/G</td>
<td>A/G</td>
<td>DMET, SNP6/500K, and GoldenGate</td>
</tr>
<tr>
<td>3</td>
<td>rs2274407</td>
<td>ABCC4</td>
<td>G/G</td>
<td>T/G</td>
<td>None available</td>
<td>None available</td>
<td>None concordant</td>
</tr>
<tr>
<td>1</td>
<td>rs2266780</td>
<td>FM03</td>
<td>A/A</td>
<td>None available</td>
<td>G/A</td>
<td>None available</td>
<td>None concordant</td>
</tr>
<tr>
<td>4</td>
<td>rs2266780</td>
<td>FM03</td>
<td>A/A</td>
<td>None available</td>
<td>G/A</td>
<td>None available</td>
<td>None concordant</td>
</tr>
<tr>
<td>5</td>
<td>rs2266780</td>
<td>FM03</td>
<td>A/A</td>
<td>None available</td>
<td>G/A</td>
<td>None available</td>
<td>None concordant</td>
</tr>
<tr>
<td>6</td>
<td>rs1800440</td>
<td>CYP1B1</td>
<td>A/G</td>
<td>None available</td>
<td>G/G</td>
<td>None available</td>
<td>None concordant</td>
</tr>
<tr>
<td>7</td>
<td>rs1800440</td>
<td>CYP1B1</td>
<td>A/A</td>
<td>None available</td>
<td>G/A</td>
<td>None available</td>
<td>None concordant</td>
</tr>
</tbody>
</table>

DMET, Drug Metabolizing Enzymes and Transporters Plus array; SNP, single-nucleotide polymorphism.

<table>
<thead>
<tr>
<th>Genes</th>
<th>No. of variants on DMET passing QC (call rate + HWE)</th>
<th>Median of call rates for all variants in gene</th>
<th>Methods used in addition to DMET Plus</th>
<th>No. of samples typed by at least 1 orthogonal method</th>
<th>Total no. of SNP–patient samples typed</th>
<th>No. of discordant genotypes</th>
<th>% Concordant</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT</td>
<td>8</td>
<td>99.9</td>
<td>Sanger sequencing, Prometheus, GoldenGate</td>
<td>67, 215, 32</td>
<td>906</td>
<td>2</td>
<td>99.8</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>26</td>
<td>99.8</td>
<td>Sanger sequencing</td>
<td>67</td>
<td>268</td>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>15</td>
<td>98.1</td>
<td>Sanger sequencing, GoldenGate</td>
<td>67, 32</td>
<td>431</td>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>16</td>
<td>98.4</td>
<td>Sanger sequencing, GoldenGate</td>
<td>67, 32</td>
<td>230</td>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td>VKORC1</td>
<td>21</td>
<td>99.2</td>
<td>SNP6/500K, Sanger sequencing, GoldenGate</td>
<td>88, 67, 32</td>
<td>608</td>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td>DPYD</td>
<td>15</td>
<td>98.5</td>
<td>Sanger sequencing, GoldenGate</td>
<td>67, 32</td>
<td>165</td>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>30</td>
<td>99.3</td>
<td>SNP6/500K, Sanger sequencing, GoldenGate</td>
<td>88, 67, 32</td>
<td>626</td>
<td>1</td>
<td>99.8</td>
</tr>
<tr>
<td>SLC01B1</td>
<td>17</td>
<td>99.5</td>
<td>SNP6/500K, MassARRAY, GoldenGate</td>
<td>88, 31, 32</td>
<td>565</td>
<td>0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

DMET, Drug Metabolizing Enzymes and Transporters Plus array; HWE, Hardy–Weinberg equilibrium; SNP, single-nucleotide polymorphism.
PG4KDS: use array to test for 225 genes
Use process to move one gene/drug pair at a time into medical record
Back up with decision-support for prescribing

Determine eligibility for migrating individual test results

Start: 
TPMT
CYP2D6

Process for migrating PG data to medical record
PG4KDS process

Pt enrolled

DNA genotyped

Genotypes classified as clinically eligible genotypes (CEGs), research only, conflict, or suspect

Most genotypes remain in research database

Ongoing evaluations of data by experts

Evaluation of genotype/drug phenotype, and genotype/incidental findings, at least annually

A small fraction of CEGs that meet threshold for Clinical Pharmacogenetic Loci

Clinical Pgen Loci genotypes posted as lab results in medical record with basic Pgen consult

Subset of selected genotypes linked to drug orders, problem list via Decision Support

Evaluation of decision support flags at least annually
**CYP2D6**: 48 diplotypes observed in 220 patients

<table>
<thead>
<tr>
<th>Diploype &amp; CN</th>
<th>% Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*2(x2)</td>
<td>15.66%</td>
</tr>
<tr>
<td>*1/*1(x2)</td>
<td>13.13%</td>
</tr>
<tr>
<td>*1/*4(x2)</td>
<td>8.59%</td>
</tr>
<tr>
<td>*2/*2(x2)</td>
<td>8.59%</td>
</tr>
<tr>
<td>*2/*4(x2)</td>
<td>5.05%</td>
</tr>
<tr>
<td>*1/*41(x2)</td>
<td>4.55%</td>
</tr>
<tr>
<td>*1/*1(x1)</td>
<td>3.03%</td>
</tr>
<tr>
<td>*1/*9(x2)</td>
<td>3.03%</td>
</tr>
</tbody>
</table>
Create Look-up Tables to Link Diplotypes

- To phenotype
- Classify phenotype as routine or priority
- Link to appropriate consult
- Link high-risk diplotypes to Clinical Decision Support Alerts
## CYP2D6 Look-up Reference Table
Copy Number, Diplootype, and Activity Score

<table>
<thead>
<tr>
<th>CN</th>
<th>Diplootype</th>
<th>Diplootype in Milli (Result)</th>
<th>Activity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>*5/*5</td>
<td>(*5/*5)0N</td>
<td>0.0</td>
</tr>
<tr>
<td>1</td>
<td>*1/*5</td>
<td>(*1/*1)1N</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>*2/*5</td>
<td>(*2/*2)1N</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>*1/*1,*1/*9,*9/*9</td>
<td>(*1/*1,*1/*9,*9/*9)1N</td>
<td>1.0 or 0.5</td>
</tr>
<tr>
<td>1</td>
<td>*41/*5</td>
<td>(*41/*41)1N</td>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
<td>*17/*17,*17/*40,*40/*40</td>
<td>(*17/*17,*17/*40,*40/*40)1N</td>
<td>0.5 or 0.0</td>
</tr>
<tr>
<td>1</td>
<td>*4/*5</td>
<td>(*4/*4)1N</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>*1/*1</td>
<td>(*1/*1)2N</td>
<td>2.0</td>
</tr>
<tr>
<td>2</td>
<td>*1/*10</td>
<td>(*1/*10)2N</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>*1/*17</td>
<td>(*1/*17)2N</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>*1/*2</td>
<td>(*1/*2)3N</td>
<td>3.0</td>
</tr>
<tr>
<td>2</td>
<td>*1/*3</td>
<td>(*1/*3)2N</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>*1/*41</td>
<td>(*1/*41)2N</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>*1/*6</td>
<td>(*1/*6)2N</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Table 1. Assignment of likely codeine metabolism phenotypes based on *CYP2D6* diplotypes

<table>
<thead>
<tr>
<th>Likely phenotype (^a)</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>An individual carrying more than two copies of functional alleles</td>
<td>*1/*1(\times)(N), *1/*2(\times)(N)</td>
</tr>
<tr>
<td>(~1-2% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>1.0-2.0</td>
<td>An individual carrying two alleles encoding full or reduced function; or one full function allele together with either one non-functional or one reduced function allele</td>
<td>*1/*1, *1/*2, *2/*2, *1/*4(\times), *1/*4, *2/*5, *10/*10</td>
</tr>
<tr>
<td>(~77-92% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>0.5</td>
<td>An individual carrying one reduced and one non-functional allele</td>
<td>*4/*10, *5/*41</td>
</tr>
<tr>
<td>(~2-11% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>0</td>
<td>An individual carrying no functional alleles</td>
<td>*4/*4, *4/*5, *5/*5, *4/*6</td>
</tr>
<tr>
<td>(~5-10% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Activity scores from Crews et al., Clin Pharmacol Ther 2012


Crews et al., Clin Pharmacol Ther 2012
## Translate phenotypes into EMR priority status

<table>
<thead>
<tr>
<th>CYP2D6 phenotype</th>
<th>CYP2D6 EMR Flag</th>
<th>Post-test Alerts fire to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid metabolizer</td>
<td>Priority</td>
<td>All clinicians ordering codeine</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Priority</td>
<td>All clinicians ordering codeine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TPMT phenotype</th>
<th>TPMT EMR Flag</th>
<th>Post-test Alerts fire to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygote</td>
<td>Priority</td>
<td>All clinicians ordering a thiopurine</td>
</tr>
<tr>
<td>Homozygous variant</td>
<td>Priority</td>
<td>All clinicians ordering thiopurine</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Priority</td>
<td>All clinicians ordering thiopurine</td>
</tr>
</tbody>
</table>
Decision Support

- Genotyping results, interpretation of haplotypes assignment of metabolizer status in the context of a specific drug are complex.

- Electronic decision support incorporated into EMR are critical tools

  Pre – and post alert systems
Pre-Alert: Direct to PGX test if indicated

PGEN TESTING

TPMT genotype test is recommended before using a thiopurine (mercaptopurine, thioguanine, and azathioprine). A TPMT genotype test does not appear to have been ordered for this patient.

Alert Action
- cancel
- continue

Add Order for:
- TPMT Genotype → T.N. Collect Now. Blood, ONCE
In Cerner, High-risk genotypes are entered into EMR in Problem List

Decision support:
Links high-risk genotypes to drug ordering, prescribing, and administration

For high priority diplotypes, enter trigger for decision support alerts
Post-test: If a clinician selects a medication that is linked to the specific PGEN alert, Decision support-based Warning Box appears. The clinician is then directed to select an appropriate action before proceeding.
***PHARMACOGENETICS CONSULT FOR***
*CYP2D6 GENOTYPE*

Sample for CYP2D6 Genotype obtained: $SAMPLE_DT_TM
PG4KDS CYP2D6 Genotype Result: (*4/*4)1N

Based on the genotype result this patient is predicted to be a poor metabolizer of CYP2D6 substrates. This patient may require either a dose adjustment of any drug metabolized by CYP2D6 or a therapeutic alternative.

The CYP2D6 genotype result of *4/*4 with a copy number of 1 is equivalent to *4/*5. A result of *4/*5 signifies that the patient has one copy of a non-functional (*4) allele and one deleted (*5) allele. This patient may be at a high risk for an adverse or poor response to medications that are metabolized by CYP2D6. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by the CYP2D6 enzyme pathway. If codeine is prescribed to a poor metabolizer, suboptimal analgesia is very likely; therefore a therapeutic alternative is recommended. The diplotype result equates to a CYP2D6 activity score of 0. For more information about specific medications metabolized by CYP2D6, please go to www.stjude.org/pg4kds.

Comments: none_
***PHARMACOGENETICS CONSULT FOR***
* CYP2D6 GENOTYPE *

Sample for CYP2D6 Genotype Obtained:
9/22/2011
PG4KDS CYP2D6 Genotype Result: (*1/*1)2N

Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2D6 substrates.

This result signifies that the patient has two copies of a wild-type (normal function) allele. The expected phenotype suggests that there is no reason to selectively adjust the dose of most medications (including codeine) that are metabolized by the CYP2D6 enzyme pathway. The diplotype result equates to a CYP2D6 activity score of 2. For more information about specific medications metabolized by CYP2D6, please go to www.stjude.org/pg4kds.

Phenotype Assignment (6 versions)

Diploptype Interpretation (32 versions)

Dosing Recommendations (6 versions)

Activity Score (11 versions)

Educational Link

### CYP2D6 Consult: Section 1

<table>
<thead>
<tr>
<th>Section</th>
<th>Version Code</th>
<th>Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype Assignment</td>
<td>1A</td>
<td>Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2D6 substrates.</td>
</tr>
<tr>
<td>Phenotype Assignment</td>
<td>1B</td>
<td>Based on the genotype result this patient is predicted to be an intermediate metabolizer of CYP2D6 substrates. This patient may require a dose adjustment to any drug metabolized by CYP2D6.</td>
</tr>
<tr>
<td>Phenotype Assignment</td>
<td>1C</td>
<td>Based on the genotype result this patient is predicted to be a poor metabolizer of CYP2D6 substrates. This patient may require either a dose adjustment of any drug metabolized by CYP2D6 or a therapeutic alternative.</td>
</tr>
<tr>
<td>Phenotype Assignment</td>
<td>1D</td>
<td>Based on the genotype result this patient is predicted to be an ultra-rapid metabolizer of CYP2D6 substrates. This patient may require either a dose adjustment to any drug metabolized by CYP2D6 or a therapeutic alternative.</td>
</tr>
<tr>
<td>Phenotype Assignment</td>
<td>1TT</td>
<td>Based on the genotype result this patient is predicted to be either an extensive or ultra-rapid metabolizer of CYP2D6 substrates; the genotype assay yielded ambiguous results. Because there is a chance this patient has ultra-rapid metabolism, the patient may require either a dose adjustment to any drug metabolized by CYP2D6 or a therapeutic alternative.</td>
</tr>
<tr>
<td>Phenotype Assignment</td>
<td>1FFF</td>
<td>The expected phenotype and activity score for this patient cannot be determined due to failure of the genotype test. Please consult with a clinical pharmacist for further information, and the possibility of performing another genotype test.</td>
</tr>
</tbody>
</table>
## Section 2

<table>
<thead>
<tr>
<th>Section</th>
<th>Version Code</th>
<th>Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diploype Interpretation</td>
<td>2E</td>
<td>This result signifies that the patient has two copies of a wild-type (normal function) allele.</td>
</tr>
<tr>
<td>Diploype Interpretation</td>
<td>2F</td>
<td>This result signifies that the patient has one copy of a wild-type (normal function) allele and one copy of a reduced function allele.</td>
</tr>
<tr>
<td>Diploype Interpretation</td>
<td>2G</td>
<td>This result signifies that the patient has one copy of a wild-type (normal function) allele and one copy of a non-functional allele.</td>
</tr>
<tr>
<td>Diploype Interpretation</td>
<td>2H</td>
<td>This result signifies that the patient has two copies of a reduced function allele.</td>
</tr>
<tr>
<td>Diploype Interpretation</td>
<td>2I</td>
<td>This result signifies that the patient has one copy of a reduced function allele and one copy of a non-functional allele.</td>
</tr>
<tr>
<td>Diploype Interpretation</td>
<td>2J</td>
<td>This result signifies that the patient has two copies of a non-functional allele.</td>
</tr>
<tr>
<td>Diploype Interpretation</td>
<td>2X</td>
<td>The CYP2D6 genotype result of *2/*2 with a copy number of 1 is equivalent to *2/*5. A result of *2/*5 signifies that the patient has one copy of a wild-type (*2, normal function) allele and one deleted (*5) allele.</td>
</tr>
<tr>
<td>Section</td>
<td>Version Code</td>
<td>Version</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dosing Recommendations</td>
<td>3S</td>
<td>The expected phenotype suggests that there is no reason to selectively adjust the dose of most medications (including codeine) that are metabolized by the CYP2D6 enzyme pathway.</td>
</tr>
<tr>
<td>Dosing Recommendations</td>
<td>3T</td>
<td>This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2D6. To avoid an untoward drug response, dose adjustments may be necessary for medications metabolized by the CYP2D6 enzyme pathway. If codeine is prescribed to an intermediate metabolizer, poor analgesia may be possible, and close monitoring of response is recommended.</td>
</tr>
<tr>
<td>Dosing Recommendations</td>
<td>3U</td>
<td>This patient may be at a high risk for an adverse or poor response to medications that are metabolized by CYP2D6. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by the CYP2D6 enzyme pathway. If codeine is prescribed to a poor metabolizer, suboptimal analgesia is very likely; therefore a therapeutic alternative is recommended.</td>
</tr>
<tr>
<td>Dosing Recommendations</td>
<td>3V</td>
<td>This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2D6. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by the CYP2D6 enzyme pathway. If codeine is prescribed to an ultra-rapid metabolizer, toxic side effects are likely; therefore a therapeutic alternative is recommended.</td>
</tr>
</tbody>
</table>
# CYP2D6 Consult: Section 4

<table>
<thead>
<tr>
<th>Section</th>
<th>Version Code</th>
<th>Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity Score</td>
<td>4K</td>
<td>The diplotype result equates to a CYP2D6 activity score of 4.</td>
</tr>
<tr>
<td>Activity Score</td>
<td>4L</td>
<td>The diplotype result equates to a CYP2D6 activity score of 3.</td>
</tr>
<tr>
<td>Activity Score</td>
<td>4M</td>
<td>The diplotype result equates to a CYP2D6 activity score of 2.5.</td>
</tr>
<tr>
<td>Activity Score</td>
<td>4UU</td>
<td>The diplotype result equates to a CYP2D6 activity score of 2.5 or 2.</td>
</tr>
<tr>
<td>Activity Score</td>
<td>4N</td>
<td>The diplotype result equates to a CYP2D6 activity score of 2.</td>
</tr>
<tr>
<td>Activity Score</td>
<td>4O</td>
<td>The diplotype result equates to a CYP2D6 activity score of 1.5.</td>
</tr>
<tr>
<td>Activity Score</td>
<td>4P</td>
<td>The diplotype result equates to a CYP2D6 activity score of 1. As guidelines for gene-drug pairs evolve, it is possible that for certain medications, doses will need to be selectively adjusted for patients with this activity score.</td>
</tr>
</tbody>
</table>

**Educational Link**

5CCC For more information about specific medications metabolized by CYP2D6, please go to www.stjude.org/pg4kds.
Gene Diplotype Version Code

<table>
<thead>
<tr>
<th>Gene</th>
<th>Diplotype</th>
<th>Version Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>*5/*5</td>
<td>1C, 2GG, 3U, 4R, 5CCC, 6GGG</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*1/*5</td>
<td>1A, 2W, 3S, 4P, 5CCC, 6GGG</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*2/*5</td>
<td>1A, 2X, 3S, 4P, 5CCC, 6GGG</td>
</tr>
</tbody>
</table>

Code Version

<table>
<thead>
<tr>
<th>Code</th>
<th>Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>1C</td>
<td>Based on the genotype result this patient is predicted to be a poor metabolizer ...</td>
</tr>
<tr>
<td>1A</td>
<td>Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2D6 substrates.</td>
</tr>
<tr>
<td>2GG</td>
<td>A result of *5/*5 signifies both CYPD2D6 alleles are deleted in this patient.</td>
</tr>
<tr>
<td>2W</td>
<td>The CYP2D6 genotype result of *1/*1 with a copy number of 1 is equivalent to *1/*5. A result of *1/*5 signifies ...</td>
</tr>
<tr>
<td>2X</td>
<td>The CYP2D6 genotype result of *2/*2 with a copy number of 1 is equivalent to *2/*5. A result of *2/*5 signifies ...</td>
</tr>
<tr>
<td>3U</td>
<td>This patient may be at a high risk for an adverse or poor response to medications that are metabolized by CYP2D6. ...</td>
</tr>
<tr>
<td>3S</td>
<td>This signifies the patient has an additional copy of either a wild-type (normal function) allele or a non-functional allele. ...</td>
</tr>
</tbody>
</table>

**Priority CYP2D6-Drug Pairs**

PharmGKB curators identified a list of priority drugs metabolized by CYP2D6 for development of dosing guidelines and clinical decision support alerts.

<table>
<thead>
<tr>
<th>Tricyclics (amitriptyline, nortriptyline)</th>
<th>Flecainide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Zuclopenthixol</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Clomipramine</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Carvedilol</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Atomoxetine</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Clozapine</td>
</tr>
</tbody>
</table>
Resources: Genotyping

Genetic Testing Reference Materials Program

Initiative coordinated by the CDC

Center for Surveillance, Epidemiology, and Laboratory Services
Division of Laboratory Programs, Standards, and Services
Lisa Kalman, PhD

- Improve and coordinate information exchange about reference materials
- Monitor reference material needs of genetic testing community
- Facilitate submission, development and characterization of reference materials
- Develop a sustainable community process for continued reference material development
Study Design:

DNA from 137 Coriell cell lines are being characterized in 10 labs with a number of PGx platforms

- Affymetrix DMET (231 genes, 1931 SNPs)
- Sequenom iPLEX ADME (36 genes)
- Sequenom iPLEX expanded panels (CYP2D6, CYP2C19, VKORC1, UGT1A1)
- AutoGenomics (CYP2D6, CYP3A4, CYP3A5, NAT2)
- GenMark (CYP2C19, CYP3A4/3A5, CYP2C9/VKORC1)
- Luminex (CYP2D6, CYP2C19, CYP2C9/VKORC1)
- Roche Amplichip (CYP2D6, CYP2C19)
- Targeted NGS assays – 3 labs
- LifeTech Ion Torrent NGS assay- 2 labs
GeT-RM Pharmacogenetics

- Genotype data will be compiled and a consensus genotype will be determined for each cell line
  - 2 phases of data analysis/release:
    - SNP genotypes, haplotypes
    - sequence data

- Data will be published and available on GeT-RM website

- Data will be displayed in a searchable database
Resources

CPIC: Clinical Pharmacogenetics Implementation Consortium

<table>
<thead>
<tr>
<th>Host Institution</th>
<th>PharmGKB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Email</td>
<td><a href="mailto:cpic@pharmgkb.org">cpic@pharmgkb.org</a></td>
</tr>
</tbody>
</table>

Drug(s): Azithromycin; Mecaptopurine; Thiopurine; Clopidogrel; Warfarin; Codeine; Captopril; Abacavir; Carbamazepine; Phenytoin; Allopurinol; Rasburicase; Pidotenic; Simvastatin

Related Links: Publications

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed in late 2009, as a shared project between PharmGKB and the Pharmacogenomics Research Network. CPIC guidelines are peer-reviewed and published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous posting to PharmGKB with supplemental information/data and updates. Anyone with clinical interests in pharmacogenetics is eligible for membership. CPIC's goal is to address some of the barriers to implementation of pharmacogenetic tests into clinical practice.

BACKGROUND

One barrier to clinical implementation of pharmacogenetics is the lack of freely available, peer-reviewed, updatable, and detailed gene/drug clinical practice guidelines. CPIC provides guidelines that enable the translation of genetic laboratory test results into actionable prescribing decisions for specific drugs. The guidelines can center on genes (e.g., thiopurine methyltransferase and its implications for thiopurines) or around drugs (e.g., warfarin and CYP2C9 and VKORC1). Priority is given to genotyping tests that are already offered in CLIA-approved clinical settings.

CPIC GUIDELINES

CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered. A key assumption underlying the CPIC guidelines is that clinical high-throughput and pre-emptive (pre-prescription) genotyping will become more widespread, and that clinicians will be faced with having patients' genotypes available even if they have not explicitly ordered a test with a specific drug in mind. Each CPIC guideline adheres to a standard format, and includes a standard system for grading levels of evidence linking genotypes to phenotypes, how to assign phenotypes to clinical genotypes, dosing recommendations based on genotype/phenotype, and a standard system for assigning strength to each dosing recommendation.

- View CPIC guidelines published on PharmGKB.
- View the list of CPIC guideline PubMed citations.
- View the current list of gene/drug pairs of interest that are already, or will be, the subject of CPIC guidelines.

http://www.pharmgkb.org/page/cpic
Resources

PharmGKB will be unavailable November 2nd & 3rd. This is a planned update to our servers and they will be offline temporarily. We will be back up as soon as possible.

Search PharmGKB: 

CPIC publishes guidelines for IFNL3(III.2BB) genotype with peginterferon alpha based regimens

CPIC: Implementing PGx

Clinical Pharmacology & Therapeutics

PharmGKB Knowledge Pyramid

PGx-Based Drug Dosing Guidelines

- IFNL3 (III.2BB) containing and ribavirin article and supplement.
- DPYD/capetibine, 5FU and tegafur article and supplement.
- more guidelines.

CPIC Gene-Drug Pairs

TPP Gene Tables

PGx Research

- VIP: Very Important PGx gene summation
- View PharmGKB pathways
- Alphabetically
- By therapeutic category
- Annotated SNPs by gene
- Drugs with genetic information
Collaborations

The InforMED Kids Study
PI: Shannon Manzi, PharmD

Background
Renal Transplant, Epilepsy and the Inflammatory Bowel Disease programs have agreed to participate
Goal is to enroll 1000 patients over two years

What are we doing
Genotyping samples on broad commercially available platform via partnership with Medical College of Wisconsin (MCW)
Collecting phenotype data studying the genotype and phenotype data collected for drug/gene pair analysis
Returning results to indicated providers
Collaborations

Medication Therapy Management (MTM) and Pharmacogenetic Testing (PGx)

PI: Susanne Haga, PhD

• Study Goals
  Assess benefit of PGx testing as part of MTM service
  Assess feasibility of pharmacist-delivered PGx testing in clinical setting as part of MTM

• Study Design
  Observational study
  DMET array performed by MCW
  Two pharmacist-conducted MTM sessions with recommendations guided by PGx results
  Participant surveys at baseline 3 month follow-up

• Primary outcome measures
  To assess benefit of PGx + MTM
  To assess feasibility
Pre-emptive Genotyping: Pros and Cons

The pros

• Having important lab test available when important decisions need to be made delivers better care
• Pre-emptive genotyping is feasible and cost effective
• Extensive research results support the decision process
• Available results will increase acceptance of PGX

The cons

• Genotyping is the easy part - Implementation is the challenge
Pre-emptive Genotyping: Lessons learned

• We continue to learn…

• Implementation is site specific
  clinical needs, patient populations

• Capture opinion leaders
• Needs assessment
• Education, collaboration, continued evaluation
• Multidisciplinary teams:
  Clinical Lab
  Pharmacy
  PGX experts
  Physician
  Medical record/EMR
The Challenges Ahead of Us

• Integrate the avalanche of data into medical records
• Actionable data points?
• Access to data JIT – at the time of care
• What is the function?
Acknowledgement

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Nissa Lambert

Diane Linzmeier
Susan Pachowitz
Paula Engelking

Sandy Grieger

David Bick
Gunter Scherer
Jayme Wittke
Brett Chirempes
Science Webinar Series
Using Pharmacogenetic Markers in Clinical Treatment: The Pros and Cons of Preemptive Genetic Testing

6 November 2013

Brought to you by the Science/AAAS Custom Publishing Office

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Medical College of Wisconsin
Milwaukee, WI

Moderator:

Sean Sanders, Ph.D.
Science/AAAS
Washington, DC

Q & A

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