Clinical Implementation of Pharmacogenetics

Mary V. Relling, Pharm.D.
St. Jude Children’s Research Hospital, Memphis, USA
Pharmacogenetic Discovery vs implementation

• Discovery of host and treatment risk factors for adverse outcomes in ALL: relapse and adverse drug effects (osteonecrosis)
  – Better understand mechanism and means to avoid
  – Discover and validate tests for eventual clinical use

• Implement pharmacokinetic, pharmacodynamic, and pharmacogenetic tests for patient care
Discovery of pharmacogenetic genotype/phenotype associations is ongoing----but are there pharmacogenetic tests we should be implementing in the clinic now?
When to use a test to guide prescribing?

• When getting prescribing right is important
When to use a test to guide prescribing?

• Safety: drug has a narrow therapeutic index
• Efficacy: effective treatment of disease is important
• Dosing to pharmacodynamic effects is not readily titratable via other means
• Drug that needs a test has some advantages over other drugs that don’t
When to use a test to guide prescribing?

• Safety: drug has a narrow therapeutic index
  – Difference between dose of drug needed to cause intended effect is not much lower than doses that can cause serious effects
    • e.g. cytotoxic anticancer drugs vs amoxicillin or levothyroxine
  – Unpredictable, non-dose related adverse effects
    • e.g. Stevens-Johnson syndrome and carbamazepine vs drowsiness from benzodiazepines
When to use a test to guide prescribing?

- **Efficacy**: effective treatment of disease is important life-saving
  - e.g. anticancer drugs, anticonvulsants vs antihistamines for seasonal allergies
When to use a test to guide prescribing?

• Dosing to pharmacodynamic effects is not readily titratable via other means
  – E.g. many anticancer drugs, depression, schizophrenia vs cholesterol, blood pressure, diabetes
  – Especially a problem when multiple drugs on board with overlapping toxicities
When to use a test to guide prescribing?

• Drug that needs a test has some advantages over other drugs that don’t
  – e.g. codeine over morphine, ondansetron over granisetron
10% of the population believe Codeine is the same as placebo. 90% of the population believe it is effective. Poulsen et al. (1996) indicate that Codeine is too active for 1-2% of the population.


And too active for 1-2% of the population.
12% of the population should not take codeine based on CYP2D6

- Intermediate Metabolizer-low or no activity
- Poor Metabolizer-lower activity
- Ultra-rapid Metabolizer-very high activity
- Extensive Metabolizer-normal activity

78% of the population is classified as Extensive Metabolizer.

2% of the population is classified as Ultra-rapid Metabolizer, which is indicated by the red codeine symbol with a red cross through it.
Why Bother with Codeine at All?

As of 2015, only Schedule III opioid available in US
But genetic testing for this and other drugs remains extremely uncommon....
We are approaching implementation of clinical pharmacogenetics on 2 fronts

Long-term goal: preemptive pharmacogenetic testing as the standard of care... for everyone All CPIC guidelines.
Survey: top 3 challenges to implementing pharmacogenetics in the clinic

• 95% of respondents selected: “process required to translate genetic information into clinical actions”

• Next 2 responses
  – Genotype test interpretation (e.g. using genotype information to assign phenotype)
  – Providing recommendations for selecting the drug/gene pairs to implement

• formed in late 2009 as a shared project between PharmGKB and the PGRN
• CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy.
  – Not WHETHER tests should be ordered.
• Key Assumption:
  – Clinical high-throughput and pre-emptive genotyping will become more widespread.
  – Clinicians will be faced with having patients’ genotypes available even if they did not order test with drug in mind.
CPIC level A (high or moderate actionability) guideline genes (n=14) and drugs, Feb 2016

- **TPMT**
  - MP, TG, azathioprine

- **CYP2D6**
  - Codeine, tramadol, hydrocodone, oxycodone, TCAs

- **CYP2C19**
  - TCAs, clopidogrel, voriconazole

- **VKORC1**
  - warfarin

- **CYP2C9**
  - Warfarin, phenytoin

- **HLA-B**
  - Allopurinol, CBZ, abacavir, phenytoin

- **CFTR**
  - ivacaftor

- **DPYPD**
  - 5FU, capecitabine, tegafur

- **G6PD**
  - rasburicase

- **UGT1A1**
  - Irinotecan, atazanavir

- **SLCO1B1**
  - simvastatin

- **IFNL3 (IL28B)**
  - interferon

- **CYP3A5**
  - Tacrolimus

- **RYR1**
  - NM blockers

[https://www.pharmgkb.org/page/cpicGeneDrugPairs](https://www.pharmgkb.org/page/cpicGeneDrugPairs)
How do we impose some order on process of deciding what to implement in the clinic, and when?
Initial prioritization considerations for new gene/drug groups

*may change over time as evidence and experience accumulates*

**New gene(s) / drug(s)**

- Gene already subject to CPIC guideline
  - Actionable in Dutch or other professional society guidelines
    - Evaluate alternatives, evidence
      - CPIC level A or B: prescribing action recommended; alternative therapies or dosing are highly likely to be effective and safe
- Gene not yet subject to CPIC guideline
  - Nominated by CPIC member or outside advocate like FDA labeling
    - Evaluate alternatives, evidence
      - CPIC level C: no prescribing action recommended; alternatives are unclear, but testing is common
  - PharmGKB annotation level 1A, 1B, 2A or 2B
    - Evaluate alternatives, evidence, degree of testing
      - CPIC level D: (PharmGKB annotation) no prescribing action recommended; alternatives are unclear or evidence is weak; testing is rare or nonexistent

Guidelines: 20 level A, 9 level B 20 level C 60-100 level D
Evidence considered for clinical implementation of pharmacogenetic testing: gene/drug specific

- Association of the genetic variation with drug effect----GWAS can contribute here
- randomized clinical studies of genetically-based prescribing outcomes versus “standard of care”
- pre-clinical and clinical studies linking pharmacologic effects or drug concentrations to genomic variation
- case reports
- in vivo PK or other functional studies
- in vitro functional studies

Caudle et al, Current Drug Metab 2014
Evidence considered for clinical implementation of pharmacogenetic testing: extra gene/drug

- therapeutic index for the drug(s)
- severity of underlying disease
- consequences of suboptimal prescribing
- availability of genetic tests
- availability of and evidence for alternative therapy

Caudle et al, *Current Drug Metab* 2014
Clopidogrel requires CYP2C19 to be activated in liver; CYP2C19 was candidate gene for clopidogrel’s antiplatelet effect
GWAS for platelet aggregation response to clopidogrel confirmed importance of $CYP2C19$ genetic variation

Shuldiner et al JAMA 2009
More CV events in those with *CYP2C19*2 inactive alleles

Shuldiner et al JAMA 2009
Evidence considered for clinical implementation of pharmacogenetic testing: *extra gene/drug*

- therapeutic index for the drug(s)
  - Bleeding vs thrombosis
- severity of underlying disease
  - Stroke, myocardial infarction
- consequences of suboptimal prescribing
  - Death, serious morbidity
- availability of genetic tests
  - yes
- availability of and evidence for alternative therapy
  - yes

Caudle et al, *Current Drug Metab* 2014
Clinical Pharmacogenetics Implementation Consortium Guidelines for \textit{CYP2C19} Genotype and Clopidogrel Therapy: 2013 Update

SA Scott\textsuperscript{1}, K Sangkuhl\textsuperscript{2}, CM Stein\textsuperscript{3}, J-S Hulot\textsuperscript{4,5}, JL Mega\textsuperscript{6}, DM Roden\textsuperscript{7}, TE Klein\textsuperscript{2}, MS Sabatine\textsuperscript{6}, JA Johnson\textsuperscript{8,9,10} and AR Shuldiner\textsuperscript{11,12}

\begin{center}
\begin{tikzpicture}

% Diagram content

\node (start) {Considering antiplatelet therapy with clopidogrel for ACS/PCI};
\node (genotype) [below of=start] {\textit{CYP2C19} genotype results\textsuperscript{1}};
\node (um) [below left of=genotype] {UM \((*1/*17, *17/*17)\)}; \node (standard) [below of=um] {Standard dosing of clopidogrel};
\node (em) [below right of=genotype] {EM \((*1/*1)\)};
\node (im) [right of=em] {IM \((*1/*2, 1/*3)\)}; \node (pm) [right of=im] {PM \((2/*2, 2/*3, 3/*3)\)};
\node (alternative) [right of=im] {Consider alternative antiplatelet agent (e.g., prasugrel, ticagrelor)\textsuperscript{2}};

\draw[->] (start) -- (genotype);
\draw[->] (genotype) -- (um) node[midway, below] {};
\draw[->] (genotype) -- (em) node[midway, below] {};
\draw[->] (genotype) -- (im) node[midway, below] {};
\draw[->] (genotype) -- (pm) node[midway, below] {};
\draw[->] (pm) -- (alternative) node[midway, below] {};
\end{tikzpicture}
\end{center}
Alternatives may be unclear: example CYP2D6 and tamoxifen
Lower disease-free survival in pts with breast CA treated with tamoxifen with CYP2D6 deficient genotype; but alternative therapy not clear (for some pts)

17 genes, 86 drugs with pharmacogenetically-based prescribing

<table>
<thead>
<tr>
<th>Number of current and planned CPIC genes, drugs and anticipated guidelines.</th>
<th>Genes</th>
<th>Drugs</th>
<th>Anticipated number of unique guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong or Moderate prescribing action-CPIC level A</td>
<td>14</td>
<td>36</td>
<td>20 (14 published)</td>
</tr>
<tr>
<td>Optional prescribing actions-CPIC level B</td>
<td>7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50</td>
<td>9</td>
</tr>
<tr>
<td>No prescribing actions-CPIC level C</td>
<td>16&lt;sup&gt;b&lt;/sup&gt;</td>
<td>47</td>
<td>20</td>
</tr>
</tbody>
</table>

<sup>a</sup>Currently this is 3 unique genes (four are already subjects of CPIC level A guidelines).

<sup>b</sup>Currently this is 13 unique genes (three are also subject to CPIC level A or B guidelines for other drugs).
There are approximately 1200 FDA-approved medications (~1450 new drugs but ~ 250 exits)

Kinch et al

Drug Discovery Today • Volume 19, Number 8 • August 2014
How many gene/drug pairs should be used in the clinic now?

- ~ 1200 chemical entities approved as drugs

  [Graph showing percentages of FDA-approved medications and prescriptions in the United States affected or not affected by actionable pharmacogenes]

  - [Link: http://www.pharmgkb.org/page/cpicGeneDrug Pairs]

  Relling & Evans, *Nature*, 2015
99% of population has high-risk diplotype for at least one of 12 CPIC genes

98.5% of whites and 99.1% of blacks in US have at least one high-risk diplotype.

A panel to test pharmacogenes could cover the vast majority of actionable variants

Dunnenberger et al Ann Rev Pharm Tox 2015
Optimizing Drug Outcomes Through Pharmacogenetics: A Case for Preemptive Genotyping

JS Schildcrout¹,², JC Denny³,⁴, E Bowton⁵, W Gregg³,⁴, JM Pulley⁵, MA Basford⁵, JD Cowan⁶, H Xu³, AH Ramirez⁴, DC Crawford⁷, MD Ritchie⁸, JF Peterson³,⁴,⁹, DR Masys³,⁴, RA Wilke⁴,¹⁰ and DM Roden⁴,⁵,¹⁰,¹¹

54% exposed to one of 56 pgen high risk drugs in one year.....
~ 60 “Pharmacogenetically High Risk” Drugs, 13 CPIC genes

2023 of 4245 patients (48%) at St. Jude received at least one of 63 “high-risk” drugs in a 1-yr period.
At St. Jude, we can overcome (or ignore) many barriers to preemptive genotyping

- We cover all patient care costs
- We provide all medications for 5000 unique high-risk patients per year
  - ~ 80% have cancer
  - ~20% have sickle cell, HIV, and other life-threatening diseases
- We have a team approach to pt care
- We have an integrated, comprehensive EMR (Cerner) with customized decision support
Ability to genotype at lots of loci on CLIA-approved array is here and allows for pre-emptive genotyping

- Affy DMET array: over 1 million features to interrogate 1900 polymorphisms in 230 genes
  - *CYP2D6* Copy number assay
- For less money than we spend on 1-2 genes, we can interrogate 230 genes (Fernandez et al, *Clin Pharm Ther*, 2012)
  - Makes pre-emptive genotyping a possibility
  - Includes 9 CPIC genes
Aim: migrate pharmacogenetic tests from laboratory (array-based) into routine patient care, to be available preemptively

- Not whether to implement, but how
- Opened for patient accrual May 2011
- >3000 patients enrolled on the study
- Goal: all SJ pts, all CPIC gene/drug pairs

PG4KDS : CLINICAL IMPLEMENTATION OF PHARMACOGENETICS at ST. JUDE


• Don’t put results in EHR without some computational clinical decision support (CDS) to actively guide prescribing

• Updating: once result is ready for 1 patient, migrate results for all past and future pts to EHR

The process

Pt enrolled → DNA genotyped → Genotypes classified as clinically eligible genotypes (CEGs), research only, conflict, or suspect → Ongoing evaluations of data by experts

Most genotypes remain in research database → Evaluation of genotype/drug phenotype, and genotype/incidental findings, at least annually

A small fraction of CEGs that meet threshold for Clinical Pharmacogenetic Loci → Evaluation of decision support flags at least annually

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
Some steps in PG4KDS Implementation

• QC the genotype data
• Translate into machine-readable clinical test results
• Translate diplotype into phenotype
• Translate phenotype into clinical interpretations for clinicians and pts
• Link high-risk phenotypes to actions: interruptive CDS, medication review
• Develop educational materials, competencies
Q-PCR Determined Copy Number 2

Q-PCR Probe ID HS04502391_cn

Called Interpretation Code NC/PRA/NA

Called Diplotypes Possible *2/*6

Called Novel Diplotypes Possible *1/UNK,*2/UNK,*6/UNK,UNK/UNK

Copy Number Corrected Alleles Q-PCR Copy Number = 2, no correction needed.

Number Non-reference Probe Sets 7

<table>
<thead>
<tr>
<th>Probe Set ID</th>
<th>Affy Verified</th>
<th>Genome Position</th>
<th>dbSNP RS ID</th>
<th>Genotype Call</th>
<th>Contributes To Alleles</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM_12278</td>
<td>N</td>
<td>Ch22:42525134</td>
<td>rs61736512</td>
<td>NoCall</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*29</td>
<td>CYP2D6*29_1659G&gt;A(V136I)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM_12276</td>
<td>Y</td>
<td>Ch22:42525086</td>
<td>rs5030655</td>
<td>T/-</td>
<td>Ref/Var</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*6</td>
<td>CYP2D6*6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Be comprehensive for those few genes:
1. define most important variants and interrogate them
2. document what was and was not interrogated
3. call gene-centric diplotypes—not variants
All variants tested are documented in EHR.
DMET Tracker: QC, avoiding duplicates, conflicts, document problems

Check DMET genotypes against existing genotypes, gene-by-gene

<table>
<thead>
<tr>
<th>Gene</th>
<th>DMET Diplotpe</th>
<th>Existing Diplotpe</th>
<th>DMET Race</th>
<th>Clinical Race</th>
<th>DMET Gender</th>
<th>Clinical Gender</th>
<th>QC Flag</th>
<th>Suspect QC</th>
<th>EMR Priority</th>
<th>PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT</td>
<td>*1/*1</td>
<td>G/G</td>
<td>G/G</td>
<td>A/A</td>
<td>white;</td>
<td>white</td>
<td>male?(0)</td>
<td>male</td>
<td>REVIEW</td>
<td>snpchip</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*(2/*6)2N</td>
<td>*2A/*6</td>
<td>white;</td>
<td>white</td>
<td>male?(0)</td>
<td>male</td>
<td>REVIEW</td>
<td>snpchip</td>
<td>ROUTINE</td>
<td>ROUTINE</td>
</tr>
<tr>
<td>TPMT</td>
<td>*1/*1</td>
<td>G/G</td>
<td>G/G</td>
<td>A/A</td>
<td>white;</td>
<td>white</td>
<td>female(2)</td>
<td>female</td>
<td>REVIEW</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*(10/*41)2N</td>
<td>*41/NEGATIVE</td>
<td>white;</td>
<td>white</td>
<td>female(2)</td>
<td>female</td>
<td>REVIEW</td>
<td>CYP2D6</td>
<td>ROUTINE</td>
<td>ROUTINE</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*(2/*2)3N</td>
<td>*2A/*2A</td>
<td>white;</td>
<td>white</td>
<td>male?(0)</td>
<td>male</td>
<td>REVIEW</td>
<td>CYP2D6</td>
<td>PRIORITY</td>
<td>ROUTINE</td>
</tr>
<tr>
<td>TPMT</td>
<td>*1/*3A,*3B/*3C</td>
<td>G/G</td>
<td>A/G</td>
<td>A/G</td>
<td>white;</td>
<td>white</td>
<td>male?(0)</td>
<td>male</td>
<td>REVIEW</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*(2/*9)2N</td>
<td>*2A/*9</td>
<td>white;</td>
<td>white</td>
<td>female(3)</td>
<td>female</td>
<td>PASS</td>
<td></td>
<td>ROUTINE</td>
<td>ROUTINE</td>
</tr>
<tr>
<td>TPMT</td>
<td>*1/*1</td>
<td>G/G</td>
<td>G/G</td>
<td>A/A</td>
<td>white;</td>
<td>white</td>
<td>female(3)</td>
<td>female</td>
<td>PASS</td>
<td></td>
</tr>
<tr>
<td>TPMT</td>
<td>*1/*1</td>
<td>None</td>
<td>white;</td>
<td>unknown</td>
<td>male?(0)</td>
<td>male</td>
<td>REVIEW</td>
<td>race</td>
<td>ROUTINE</td>
<td>ROUTINE</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*(1/*41)2N</td>
<td>None</td>
<td>white;</td>
<td>unknown</td>
<td>male?(0)</td>
<td>male</td>
<td>REVIEW</td>
<td>race</td>
<td>ROUTINE</td>
<td>ROUTINE</td>
</tr>
</tbody>
</table>
### Quality Control Steps

Check DMET gender against self-declared gender

<table>
<thead>
<tr>
<th>Gene</th>
<th>DMET Diplotype</th>
<th>Existing Diplotype</th>
<th>DMET Race</th>
<th>Clinical Race</th>
<th>Clinical Gender</th>
<th>QC Flag</th>
<th>Suspect QC</th>
<th>EMR Priority</th>
<th>PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT</td>
<td>*1/*1</td>
<td>G/G</td>
<td>G/G</td>
<td>A/A</td>
<td>white;</td>
<td>white</td>
<td>male?0)</td>
<td>male</td>
<td>REVIEW</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>(*2/*6)2N</td>
<td>*2A/*6</td>
<td>white;</td>
<td>white</td>
<td>male?0)</td>
<td>male</td>
<td>REVIEW</td>
<td>snpchip</td>
<td></td>
</tr>
<tr>
<td>TPMT</td>
<td>*1/*1</td>
<td>G/G</td>
<td>G/G</td>
<td>A/A</td>
<td>white;</td>
<td>white</td>
<td>female2</td>
<td>female</td>
<td>REVIEW</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>(*10/*41)2N</td>
<td>*41/NEGATIVE</td>
<td>white;</td>
<td>white</td>
<td>female2</td>
<td>female</td>
<td>REVIEW</td>
<td>CYP2D6</td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>(*2/*2)3N</td>
<td>*2A/*2A</td>
<td>white;</td>
<td>white</td>
<td>male?0)</td>
<td>male</td>
<td>REVIEW</td>
<td>CYP2D6</td>
<td></td>
</tr>
<tr>
<td>TPMT</td>
<td>*1/*3A, *3B/*3C</td>
<td>G/G</td>
<td>A/G</td>
<td>A/G</td>
<td>white;</td>
<td>white</td>
<td>male?0)</td>
<td>male</td>
<td>REVIEW</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>(*2/*9)2N</td>
<td>*2A/*9</td>
<td>white;</td>
<td>white</td>
<td>female3</td>
<td>female</td>
<td>PASS</td>
<td>ROUTINE</td>
<td></td>
</tr>
<tr>
<td>TPMT</td>
<td>*1/*1</td>
<td>G/G</td>
<td>G/G</td>
<td>A/A</td>
<td>white;</td>
<td>unknown</td>
<td>female?0</td>
<td>female</td>
<td>PASS</td>
</tr>
<tr>
<td>TPMT</td>
<td>*1/*1</td>
<td>None</td>
<td>white;</td>
<td>unknown</td>
<td>male?0)</td>
<td>male</td>
<td>REVIEW</td>
<td>race</td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>(*1/*41)2N</td>
<td>None</td>
<td>white;</td>
<td>unknown</td>
<td>male?0)</td>
<td>male</td>
<td>REVIEW</td>
<td>race</td>
<td></td>
</tr>
</tbody>
</table>
At any given time, ~5-7% of results are in limbo.
111 genotypes observed for CYP2D6
> 111 *CYP2D6* diplotypes have translated into 9 phenotype groups—a few of which are actionable*
Pharmacogenetics tab added to EHR; all clinically eligible genotypes are entered, along with a gene-specific consult and letter to patient.
Result and Consult Display: default interpretation is built from ordered, standardized sentences in Consult Builder

---

1.) (Medium Importance) Result Comment by DUNNENBERGER, MARK on August 28, 2013 17:21

***PHARMACOGENETICS CONSULT FOR***

**TPMT GENOTYPE**

Sample for TPMT Genotype Obtained: 06/05/2013 10:16:00
PG4KDS TPMT Genotype Result: **1*5C**

This result signifies that this patient has one copy of a wild-type (high activity) allele and one copy of a non-functional (low activity) allele. This patient is predicted to have intermediate TPMT activity. The patient is at risk for myelosuppression with normal doses of drugs in the thiourea class (6-mercaptopurine, 6-thioguanine or azathioprine), and thus reduced starting doses may be needed. Some experts recommend lower doses of thiouracils in heterozygotes because these patients may be at a higher risk of thiourea-related late secondary cancers. For 6-mercaptopurine and azathioprine, consider starting at 30-70% of the normal dose. For example, a normal dose of 6-mercaptopurine (e.g., 75 mg/m²/day) should be reduced to 20-50 mg/m²/day. A normal dose of azathioprine (e.g., 2-3 mg/kg/day) should be reduced to 0.6 - 2.0 mg/kg/day. For thioguanine reduce the normal dose by 30-50%.

Titrating thiourea doses based on myelosuppression. In the setting of myelosuppression, and depending on other therapy, emphasis should be on reducing thiourea doses over other agents. Allow 2-4 weeks to reach steady-state after each dosage adjustment. For drug monitoring, consider obtaining a thiourea metabolite erythrocyte concentration (i.e., test name TGNRBC clinical). For more information about how TPMT activity influences thiourea dosing please go to www.stjude.org/pg4kds.

---

Kristina Myers, Pharm D manager DMR

---

A result of *10/*5 signifies that the patient has one copy of a reduced function (*10) allele and one deleted (*5) allele.
<table>
<thead>
<tr>
<th>Genotype Test Result for <em>SLCO1B1</em></th>
<th>Coded Genotype/Phenotype Summary</th>
<th>EHR Priority Result Notation</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1a/*1a</td>
<td>None</td>
<td>Normal/Routine/Low Risk</td>
</tr>
<tr>
<td>*1a/*1b</td>
<td>None</td>
<td>Normal/Routine/Low Risk</td>
</tr>
<tr>
<td>*1a/*2</td>
<td>SLCO1B1 Intermediate Function</td>
<td>Abnormal/Priority/High Risk</td>
</tr>
<tr>
<td>*1a/*3</td>
<td>SLCO1B1 Intermediate Function</td>
<td>Abnormal/Priority/High Risk</td>
</tr>
<tr>
<td>*1a/*4</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
<tr>
<td>*1a/*5</td>
<td>SLCO1B1 Intermediate Function</td>
<td>Abnormal/Priority/High Risk</td>
</tr>
<tr>
<td>*1a/*6</td>
<td>SLCO1B1 Intermediate Function</td>
<td>Abnormal/Priority/High Risk</td>
</tr>
<tr>
<td>*1a/*7</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
<tr>
<td>*1a/*8</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
<tr>
<td>*1a/*9</td>
<td>SLCO1B1 Intermediate Function</td>
<td>Abnormal/Priority/High Risk</td>
</tr>
<tr>
<td>*1a/*10</td>
<td>SLCO1B1 Intermediate Function</td>
<td>Abnormal/Priority/High Risk</td>
</tr>
<tr>
<td>*1a/*11</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
<tr>
<td>*1a/*12</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
<tr>
<td>*1a/*13</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
<tr>
<td>*1a/*14</td>
<td>SLCO1B1 Increased Function</td>
<td>None</td>
</tr>
<tr>
<td>*1a/*15</td>
<td>SLCO1B1 Intermediate Function</td>
<td>Abnormal/Priority/High Risk</td>
</tr>
<tr>
<td>*1a/*16</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
<tr>
<td>*1a/*17</td>
<td>SLCO1B1 Intermediate Function</td>
<td>Abnormal/Priority/High Risk</td>
</tr>
<tr>
<td>*1a/*18</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
<tr>
<td>*1a/*19</td>
<td>Indeterminate</td>
<td>None</td>
</tr>
</tbody>
</table>
**SLCO1B1 Genotype and Simvastatin: Point of Care Clinical Decision Support**

1. Simvastatin order initiated

2. **SLCO1B1** genetic test results on file?
   - Yes: Priority result?
     - Yes: CDS Post-test alert or notify prescriber with recommendation
     - No: No post-test alert required; continue with drug order
   - No: CDS Pre-test Alert Message (additional action may be considered)

Note: Circled numerals refer to Supplementary Table 12

---

**a, d** See Supplementary Table S12 for diplotype/phenotype specific pre- and post-test alert example.

**b** Additional actions may include ordering a pharmacogenetic test, preventing the clinician from ordering the medication or allowing the clinician to cancel out of the alert.

**c** Priority result defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.
### Supplemental Table S12. Example Implementation of this Guideline: Point of Care Clinical Decision Support

<table>
<thead>
<tr>
<th>Flow Chart Reference Point (See Supplemental Figure S3)</th>
<th>CDS Context, Relative to Genetic Testing</th>
<th>Trigger Condition</th>
<th>CDS Alert Text&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre-Test</td>
<td>No SLCO1B1 result on file</td>
<td>SLCO1B1 diploptye may be important for simvastatin side effects. An SLCO1B1 genotype does not appear to have been ordered for this patient. Use of an alternative statin or dose may be recommended. Please consult a clinical pharmacist&lt;sup&gt;b&lt;/sup&gt; for more information.</td>
</tr>
<tr>
<td>2</td>
<td>Post-Test</td>
<td>SLCO1B1 - Intermediate Function</td>
<td>Based on the genotype result, this patient is predicted to have intermediate SLCO1B1 function and may be at increased risk for developing simvastatin-associated myopathy. Consider starting with a lower dose of simvastatin (20 mg/day for adults) or choosing an alternate statin agent. Monitor creatine kinase levels routinely. Please consult a clinical pharmacist&lt;sup&gt;b&lt;/sup&gt; for more information.</td>
</tr>
<tr>
<td>2</td>
<td>Post-Test</td>
<td>SLCO1B1 - Low Function</td>
<td>Based on the genotype result, this patient is predicted to have low SLCO1B1 function and may be at high risk for developing simvastatin-associated myopathy. Consider starting with a lower dose of simvastatin (20 mg/day for adults) or choosing an alternate statin agent. Monitor creatine kinase levels routinely. Please consult a clinical pharmacist&lt;sup&gt;b&lt;/sup&gt; for more information.</td>
</tr>
</tbody>
</table>

<sup>a</sup>The specific wording of the alert text may differ among sites.

<sup>b</sup>Pharmacist, pharmacologist, or a clinician with pharmacogenetic expertise/training.
Customized Decision support “behind the scenes”:
Links high-risk diplotype to ordering of applicable high-risk drug
Each high-risk result triggers med reconciliation
Allows for manual entries into problem list

High-risk diplotype translated to phenotype, automatically populated into Problem List of EMR
## Selected Problem List Entries for Actionable Phenotypes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Problem List Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TPMT</strong></td>
<td>TPMT - INTERMEDIATE ACTIVITY&lt;br&gt;TPMT - LOW OR ABSENT ACTIVITY&lt;br&gt;TPMT - POSSIBLE INTERMEDIATE ACTIVITY</td>
</tr>
<tr>
<td><strong>CYP2D6</strong></td>
<td>CYP2D6 - POSSIBLE ULTRA-RAPID METABOLIZER&lt;br&gt;CYP2D6 - ULTRA-RAPID METABOLIZER&lt;br&gt;CYP2D6 - INTERMEDIATE METABOLIZER&lt;br&gt;CYP2D6 - POSSIBLE INTERMEDIATE METABOLIZER&lt;br&gt;CYP2D6 - POOR METABOLIZER&lt;br&gt;CYP2D6 - POSSIBLE POOR METABOLIZER</td>
</tr>
<tr>
<td><strong>SLCO1B1</strong></td>
<td>SLCO1B1 - POSSIBLE INTERMEDIATE FUNCTION&lt;br&gt;SLCO1B1 - INTERMEDIATE FUNCTION&lt;br&gt;SLCO1B1 - POSSIBLE LOW FUNCTION&lt;br&gt;SLCO1B1 - LOW FUNCTION</td>
</tr>
<tr>
<td><strong>CYP2C19</strong></td>
<td>CYP2C19 - ULTRA-RAPID METABOLIZER&lt;br&gt;CYP2C19 - INTERMEDIATE METABOLIZER&lt;br&gt;CYP2C19 - POOR METABOLIZER&lt;br&gt;CYP2C19 - POSSIBLE POOR METABOLIZER</td>
</tr>
</tbody>
</table>

Pre-test alerts contain prescribing recommendations if a patient has not been genotyped.

Absence of test result will drive the CDS; so test result must be findable.

Override alert options for pre-test alerts

Post-test alerts contain prescribing recommendations based on the patient’s genotype test result.

CDS can be driven off of test result or derivation thereof (e.g. “genetic” problem list entry or phenotype)—but the terms should be standardized to get uptake in EHRs.
EHRs do not currently have the ability to handle genomic information.

There is a lack of standards for the data, interoperability, scalability, privacy, security, and storage.

A coordinated effort of key stakeholders is needed to set these standards in order to improve patient care so that genomic information is successfully integrated into the EHR.
CPIC Phenotype Term Standardization Project: Allele function and Phenotype

- **Development**
  - Created a list of options for terms (literature review and survey to genetic testing labs)

- **Prioritization**
  - Survey 1: Experts specified their level of agreement or disagreement on a symmetric agree-disagree scale (1-4) for each set of gene terms. Experts can also list additional terms.

- **Refinement**
  - Survey 2: For each gene, retained terms in which 70% of the experts agreed or strongly agreed in Survey 1.
  - Related terms were grouped together into value sets and experts specified their level of acceptance to sets of terms for each gene/gene group (acceptable/not acceptable).

- **Consensus**
  - Survey 3-5: For each gene/gene group, retained top terms selected by experts.
  - Repeat process until 70% consensus achieved.

- **Validation**
  - After 70% consensus reached, terms were circulated to the experts again for final review and feedback (as part of survey 5).

www.cpicpgx.org
Group memberships for Delphi process surveys for pgen terms

- CPIC
- ClinVar
- PGRN
- CDC Pgx nomenclature WG
- GA4GH's Clinical WG
- ClinGen PG and data modeling WG
- IGNITE
- eMERGE
- IUPHAR
- ACMG Laboratory Standards and Guidelines Committee
- CAP Pharmacogenetics WG
- HL7 Clinical Genomics WG
- IOM's Roundtable on Translating Genomic-Based Research for Health
- AMIA genomics and translational bioinformatics WG
- European Medicines Agency
- G2MC Pharmacogenomics WG
## Final Terms-Allele function

<table>
<thead>
<tr>
<th>Term/Gene Category</th>
<th>Final Term*</th>
<th>Functional Definition</th>
<th>Example diplotypes/alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allele</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased Function</td>
<td>Function greater than normal function</td>
<td>CYP2C19*17</td>
<td></td>
</tr>
<tr>
<td>Normal Function</td>
<td>Fully functional/wild-type</td>
<td>CYP2C19*1</td>
<td></td>
</tr>
<tr>
<td>Decreased Function</td>
<td>Function less than normal function</td>
<td>CYP2C19*9</td>
<td></td>
</tr>
<tr>
<td>No Function</td>
<td>Non-functional</td>
<td>CYP2C19*2</td>
<td></td>
</tr>
<tr>
<td>Unknown Function</td>
<td>No literature describing function or the allele is novel</td>
<td>CYP2C19*29</td>
<td></td>
</tr>
<tr>
<td>Uncertain Function</td>
<td>Literature supporting function is conflicting or weak</td>
<td>CYP2C19*12</td>
<td></td>
</tr>
<tr>
<td><strong>Functional Status-all genes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased Function</td>
<td>Function greater than normal function</td>
<td>CYP2C19*17</td>
<td></td>
</tr>
<tr>
<td>Normal Function</td>
<td>Fully functional/wild-type</td>
<td>CYP2C19*1</td>
<td></td>
</tr>
<tr>
<td>Decreased Function</td>
<td>Function less than normal function</td>
<td>CYP2C19*9</td>
<td></td>
</tr>
<tr>
<td>No Function</td>
<td>Non-functional</td>
<td>CYP2C19*2</td>
<td></td>
</tr>
<tr>
<td>Unknown Function</td>
<td>No literature describing function or the allele is novel</td>
<td>CYP2C19*29</td>
<td></td>
</tr>
<tr>
<td>Uncertain Function</td>
<td>Literature supporting function is conflicting or weak</td>
<td>CYP2C19*12</td>
<td></td>
</tr>
<tr>
<td>Term/Gene Category</td>
<td>Final Term*</td>
<td>Functional Definition</td>
<td>Example diplotypes/alleles</td>
</tr>
<tr>
<td>--------------------------------------------------------------------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Phenotype-Drug Metabolizing Enzymes (CYP2C19, CYP2D6, CYP3A5, CYP2C9, TPMT, DPYD, UGT1A1)</td>
<td>Ultra-rapid Metabolizer</td>
<td>Increased enzyme activity compared to rapid metabolizers.</td>
<td>Two increased function alleles, or more than 2 normal function alleles</td>
</tr>
<tr>
<td></td>
<td>Rapid Metabolizer</td>
<td>Increased enzyme activity compared to normal metabolizers but less than ultra-rapid metabolizers.</td>
<td>Combinations of normal function and increased function alleles</td>
</tr>
<tr>
<td></td>
<td>Normal Metabolizer</td>
<td>Fully functional enzyme activity</td>
<td>Combinations of normal function and decreased function alleles</td>
</tr>
<tr>
<td></td>
<td>Intermediate Metabolizer</td>
<td>Decreased enzyme activity (activity between normal and poor metabolizer)</td>
<td>Combinations of normal function, decreased function, and/or no function alleles</td>
</tr>
<tr>
<td></td>
<td>Poor Metabolizer</td>
<td>Little to no enzyme activity</td>
<td>Combination of no function alleles and/or decreased function alleles</td>
</tr>
<tr>
<td>Phenotype-Transporters (SLCO1B1)</td>
<td>Increased Function</td>
<td>Increased transporter function compared to normal function.</td>
<td>One or more increased function alleles</td>
</tr>
<tr>
<td></td>
<td>Normal Function</td>
<td>Fully functional transporter function</td>
<td>Combinations of normal function and/or decreased function alleles</td>
</tr>
<tr>
<td></td>
<td>Decreased Function</td>
<td>Decreased transporter function (function between normal and poor function)</td>
<td>Combinations of normal function, decreased function, and/or no function alleles</td>
</tr>
<tr>
<td></td>
<td>Poor Function</td>
<td>Little to no transporter function</td>
<td>Combination of no function alleles and/or decreased function alleles</td>
</tr>
<tr>
<td>Phenotype-High risk genotype status (HLA-B)</td>
<td>Positive</td>
<td>Detection of high-risk allele</td>
<td>Homozygous or heterozygous for high-risk allele</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>High risk-allele not detected</td>
<td>No copies of high-risk allele</td>
</tr>
</tbody>
</table>
Next Steps for Standardized Terms

• Use final terms in CPIC Guidelines and in our practice
• Dissemination
  – Posted on cpicpgx.org
  – DIGITiZE implementation guide
  – LOINC terms submitted
  – Manuscript submitted
• Several groups have endorsed (e.g. AMP)
• Encourage adoption by EHR vendors and clinical labs
Genetic testing is just one step

CPIC
Clinical Pharmacogenetics Implementation Consortium

Relling & Evans, Nature, 2015
But…. there remains significant reluctance to use pharmacogenetic testing in the clinic…
“many healthcare providers follow a WHO ladder “type” approach for the treatment of pain”. Because second step of the WHO ladder includes opioids “commonly used for moderate pain (e.g., tramadol, codeine, hydrocodone, and possibly oxycodone)” that overlap with medicines to avoid (codeine and tramadol) or use with caution (oxycodone and hydrocodone), genetic testing is questioned because “the use of an unfamiliar [alternative] drug ...is likely to carry a greater risk.”
Devil’s advocate: *CYP2D6* and codeine

• Consequence of providing genetic status could be:
  
  – Never use codeine—too hard to look up genetics, so overall population pain relief is worse (either everyone uses morphine—or everyone uses NSAIDs)
  
  – Use a less effective drug (like NSAID) for all with high risk genotypes (too much hassle to use narcotics)
  
  – Ignore genetics ---”pt tolerated it well in the past”

• If we tolerate illogical prescribing practices that aren’t evidence-based, genetics won’t help
Reasons cited to NOT use genetics to guide prescribing

• Use of alternatives may create more adverse effects if not prescribed appropriately (e.g. stop using codeine and misuse other narcotics or use NSAIDs)
• To avoid testing, just stop using the drug (e.g. CBZ/phenytoin [PMID: 25355835]; codeine in children)
• Clinicians may not understand genetic test results (hets vs homozygous variants) and make wrong decisions (TPMT and thiopurines)
• “patient tolerates it fine---why change?”
• Health care dollars better spent elsewhere
• Lack of randomized prospective clinical trials comparing genetically based vs conventional prescribing
Implementation of Pharmacogenomics: Evidence Needs

Mary V. Relling and David L. Veenstra*

February 26, 2015

*The authors are participants in the activities of the IOM Roundtable on Translating Genomic-Based Research for Health.
Prospective clinical trials for all testing decisions would be problematic

• “Prescribing decisions are routinely made on the basis of imperfect evidence and on extrapolations between solid evidence of mechanisms underlying interpatient variability in drug response and unstudied clinical scenarios.”

• E.g. dosing based on liver or renal dysfunction, avoidance of drug interactions, almost all prescribing in pediatrics
CPIC level A guideline genes

- **TPMT**
  - MP, TG, azathioprine
- **CYP2D6**
  - Codeine, tramadol, hydrocodone, oxycodone, TCAs*
- **CYP2C19**
  - TCAs*, clopidogrel, voriconazole*
- **VKORC1**
  - warfarin
- **CYP2C9**
  - Warfarin, phenytoin*
- **HLA-B**
  - Allopurinol, CBZ, abacavir, phenytoin
- **CFTR**
  - ivacaftor
- **DPYD**
  - 5FU, capecitabine, tegafur
- **G6PD**
  - rasburicase
- **UGT1A1**
  - Irinotecan, atazanavir
- **SLCO1B1**
  - simvastatin
- **IFNL3 (IL28B)**
  - interferon
- **CYP3A5**
  - Tacrolimus*

Mechanism is PK for interferon 8/13

[https://www.pharmgkb.org/page/cpicGeneDrugPairs](https://www.pharmgkb.org/page/cpicGeneDrugPairs)
For pharmacogene/drug pairs with a pharmacokinetic basis

• If PK is related to drug effect, data relating genetics to PK can be used to extrapolate genetics to drug effect

• Completely analogous to using creatinine clearance to adjust acyclovir doses, bilirubin to adjust vincristine doses, and weight/BSA to adjust doses for children compared to adults
  – Requiring a randomized clinical trial comparing standard to reduced doses of acyclovir in patients with creatinine clearance of 25 ml/min/1.73m² would be unethical and a waste of precious resources
PK extrapolations for dosing decisions are ubiquitous.

**Adults and Adolescents (12 years of age and older):** 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.

**Pediatrics (3 months to 12 years of age):** 20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.

**Neonatal Herpes Simplex Virus Infections (Birth to 3 months):** 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days. In neonatal herpes simplex infections, doses of 15 mg/kg or 20 mg/kg (infused at a constant rate over 1 hour every 8 hours) have been used; the safety and efficacy of these doses are not known.

**Varicella Zoster Infections: Zoster in Immunocompromised Patients:**

**Adults and Adolescents (12 years of age and older):** 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

**Pediatrics (Under 12 years of age):** 20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

**Obese Patients:** Obese patients should be dosed at the recommended adult dose using Ideal Body Weight.

**Patients with Acute or Chronic Renal Impairment:** Refer to DOSAGE AND ADMINISTRATION section for recommended doses, and adjust the dosing interval as indicated in Table 5.

### Table 5. Dosage Adjustments for Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min/1.73 m²)</th>
<th>Percent of Recommended Dose</th>
<th>Dosing Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>100%</td>
<td>8</td>
</tr>
<tr>
<td>25 - 50</td>
<td>100%</td>
<td>12</td>
</tr>
<tr>
<td>10 - 25</td>
<td>100%</td>
<td>24</td>
</tr>
<tr>
<td>0 - 10</td>
<td>50%</td>
<td>24</td>
</tr>
</tbody>
</table>
The stronger the evidence that the gene variants affect drug PK, the lower the need for clinical trial data.
Challenges to implementing pharmacogenetics in the clinic

- Generating sufficient genotype/phenotype and clinical evidence
- Tolerating illogical prescribing practices
- Overcoming hype: “pharmacogenomic testing needs to be viewed as a tool to improve drug therapy that is incremental and affordable, rather than revolutionary and cost-saving.” (Veenstra CPT Feb 2016)
Resources for Implementers

- PG4KDS publications
- PG4KDS presentations
- PG4KDS video presentations
- PGEN competencies
- PGEN residency information

www.stjude.org/pg4kds/implement
5th Year of first ASHP accredited Pharmacogenetics Residency

Kevin Hicks
Gillian Bell
Mark Dunnenberger
Rose Gammal

Amy Pasternak
Acknowledgements

http://www.stjude.org/pg4kds/implement

https://cpicpgx.org/

Kelly Caudle
Teri Klein
James Hoffman
Michelle Carrillo

Cyrine Haidar  Ulrike Reiss
Amy Pasternak
Colton Smith
Don Baker
Wenjian Yang
Kris Crews
PK RNs
Nancy Kornegay
Uli Broeckel
Charles Mullighan
Sima Jeha
Ching-Hon Pui
William E. Evans
Torrey Sandlund
Sue Kaste
Cheng Cheng
Aditya Gaur

St. Jude Children's Research Hospital

Clinical Pharmacogenetics Implementation Consortium