Clinical Implementation of Pharmacogenomics Through a Pharmacist-Managed Service

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Objectives

1. Describe steps for incorporating pharmacogenomic testing into clinical practice.

2. Provide an example of a drug/gene pair with strong evidence for clinical utility.

3. Relate the importance of clinical decision support in incorporating clinical pharmacogenomics tests into the medical record.
Steps to Incorporate Clinical Pharmacogenomics at St. Jude Children’s Research Hospital
Steps Taken to Implement a Clinical Pharmacogenomics Service

1. Identified drugs on formulary that are metabolized by polymorphic enzymes.
2. Provided a series of ACPE seminars for pharmacists to establish competencies in pharmacogenomic consults.
3. Created a departmental policy to provide direction to pharmacists and laboratory staff in the ordering and reporting of pharmacogenomic test results.
4. Communicated the availability of tests to clinical staff.

Crews et al. *Amer J Health-Syst Pharm* 2011; 68:143
Pharmacogenetics

Announcing Clinical Pharmacogenetic Tests Available Through the Clinical Pharmacokinetics Laboratory

The Clinical Pharmacokinetics Lab of the Pharmaceutical Department has made available several clinical pharmacogenetic tests for enzymes involved in the metabolism of medications relevant to our patient population. All tests will be accompanied by a patient-specific clinical pharmacy consult. Genotypes for the following 5 genes can be ordered as clinical tests:

- **Thiopurine methyltransferase (TPMT)**. The enzyme encoded by the TPMT gene is involved in the metabolism of the drugs 5-mercaptopurine, thioguanine, and azathioprine. Starting dosage regimens containing thiopurines should be individualized based on TPMT status.

  **MILLI Order Name:** Thiopurine S Methyl Genotype

- **Cytochrome P450 2D6 (CYP2D6)**. The cytochrome P450 enzyme encoded by the CYP2D6 gene plays a primary role in the metabolism of the narcotic codeine and tricyclic antidepressants (e.g., amitriptyline and nortriptyline). Approximately 5-10% of patients receive no analgesic effect from codeine because of a CYP2D6 deficiency that precludes the necessary metabolic activation.

  **MILLI Order Name:** CYP2D6 Genotype

- **CYP2C19**. The cytochrome P450 enzyme encoded by the CYP2C19 gene metabolizes several proton pump inhibitors (e.g., omeprazole) and phenytoin.

  **MILLI Order Name:** CYP2C19 Genotype

- **CYP2C9/VKORC1 (Warfarin Sensitivity Genotype)**. The cytochrome P450 enzyme encoded by the CYP2C9 gene metabolizes warfarin. The VKORC1 gene codes for the enzyme inhibited by warfarin, vitamin K epoxide reductase. Patients with genetic variation in CYP2C9 and/or VKORC1 may need lower doses of warfarin. Both genotypes can be tested from one sample of whole blood.

  **MILLI Order Name:** Warfarin Sensitivity Genotype

- **Uridine glucuronosyltransferase 1A1 (UGT1A1)**. The enzyme encoded by the UGT1A1 gene is involved in the metabolism of bilirubin; a common polymorphism in this gene is the cause of most cases of Gilbert's syndrome (indirect hyperbilirubinemia). UGT1A1 is also involved in the metabolism of the anticancer drug irinotecan.

  **MILLI Order Name:** UGT1A1 Genotype Assay
Implementing Clinical Thiopurine Methyltransferase (TPMT) Genotyping in Acute Leukemia Patients
Thiopurine Methyltransferase (TPMT) Polymorphism affects 6MP Pharmacodynamics

HPRT → TGNs → DNA incorporation

MP → TPMT → MeMP

TPMT Activity

Percent of Population

0 5 10 15 20 25 30

wt/wt

wt/m

m/m

Intracellular TGN concentrations

0 1000 2000

Mut/Mut

Wt/Mut

Wt/Wt

- myelosuppression
- risk secondary cancer
- toxicity
- risk of relapse

Leukemia 14:567-72, 2000

AACP Annual Meeting
Prospective Pharmacogenetic Testing for TPMT to Avoid Toxicity

• Goal is to genotype every ALL patient for TPMT before the first dose of mercaptopurine or thioguanine
  • Included in standard orders for ALL patients
  • Mercaptopurine dosing recommendations based on TPMT genotype and tolerability of regimen
All clinical genotype results are posted in EMR

Cerner Millenium v2010.02. Powerchart application
Clinical Pharmacogenomics Consult Entered into EMR

Sample for TPMT genotype obtained 06/11/12. Thiopurine S Methyl Transferase Genotype Result: *1/*3A.

This result means the genotype is heterozygous. Heterozygous means intermediately low TPMT activity. This patient may be at risk for toxicity with 6-mercaptopurine and should receive no more than 60 mg/msq/day of 6-mercaptopurine pending further evaluation by a clinical pharmacist and attending Hematology/Oncology physician. If myelosuppression occurs, this result suggests that the 6-mercaptopurine dose be titrated based on WBC and ANC. Every effort should be made to keep other anticancer agent doses at protocol levels.

Time/date of Consult: 06/15/2012 15:18                Jane Smith, Pharm.D.
If a clinician selects a medication that is linked to the pharmacogenomic alert, a Warning Box will appear with a brief description of the potential problem. The clinician is then directed to select an appropriate action before proceeding.
Summary of Clinical Pharmacogenomics at St. Jude

• TDM practices have informed our approach, but key distinction exists
  – Pharmacogenomics provides a laboratory result that may improve dosage individualization—without having to give the drug first

• Implementation
  – Pharmacists interpret results, which required training
  – Applying clinical decision support in our electronic medical record is a key aspect

Crews et al. Amer J Health-Syst Pharm 2011; 68:143
Are we ready to move to more sophisticated high-throughput clinical pharmacogenomic testing?
High-throughput genotyping on CLIA-approved array is here

- Affymetrix DMET Plus array: over 1 million features to interrogate 1900 polymorphisms in 225 genes

- For the same money we spend on 2 genes, we can interrogate 225---but what to do with the other 223 results?

Sissung et al. *Pharmacogenomics* 2010; 11:260
PGEN4Kids Study: CLINICAL IMPLEMENTATION OF PHARMACOGENOMICS

Goal: migrate pharmacogenomic tests from laboratory into routine patient care, to be available pre-emptively
The process - PG4KDS

Pt enrolled → DNA genotyped → Genotypes classified as clinically eligible genotypes (CEGs), research only, conflict, or suspect → Most genotypes remain in research database → 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 → Ongoing evaluations of data by experts → Evaluation of genotype/drug phenotype, and genotype/ incidental findings, at least annually → Evaluation of decision support flags at least annually

AACCP Annual Meeting
CYP2D6 and Codeine

- CYP2D6 poor metabolizers can not activate codeine.
- CYP2D6 ultrarapid metabolizers are at risk of severe toxicity due to high morphine concentrations

CYP2D6 Phenotypes - Frequency in U.S. Population

- Poor Metabolizer - low or no activity: 10%
- Intermediate Metabolizer - lower activity: 10%
- Ultra-rapid Metabolizer - very high activity: 2%
- Extensive Metabolizer - normal activity: 78%

**PGEN4Kids** Process for an Individual Gene

- Evaluate evidence for the gene e.g., Cytochrome P450 2D6 (CYP2D6)
  - Interpret genotypes-- *2, *3, *4, etc.
  - Translate to phenotypes-- Extensive Metabolizer (EM), Intermediate Metabolizer (IM), Poor Metabolizer (PM), Ultrarapid Metabolizer (UM)
- Prioritize drugs to add-- codeine, amitriptyline
- Post genotype results to electronic medical record (EMR) for all patients who have been tested
- Write wording for automated decision support
- Educate patients, parents, clinicians
- Revise, Repeat
Automated Quality Control

DMET chip genotype & diplotype calls

Infer gender, race and compare to EMR

Compare calls to other genotyping, if available

Translate into an EMR flag, e.g., routine, priority

Translate into clinical phenotype, e.g., UM, EM

Automated Clinical Translations

Automated Aggregation into Web-based DMET Tracker Software

PG4KIDS: DMET Tracker

Translate into clinical phenotype, e.g., UM, EM

Automated Aggregation into Web-based DMET Tracker Software

To the EMR
Upon approval of CYP2D6 test result, result is automatically posted to EMR
## Automated Process for Consults

### Reference Table

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>Sentence Code</th>
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<tbody>
<tr>
<td>CYP2D6</td>
<td>*4/*4</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>
<tr>
<td>CYP2D6</td>
<td>*1/*1,*1/*9,*9/*9</td>
<td>3DDD, 5CCC, 6GGG</td>
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</tbody>
</table>

### Code | Sentence |
<table>
<thead>
<tr>
<th></th>
<th></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 *4/*4 signifies this patient has inherited 2 non-functional alleles.</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>

Individualized consults are built by section based on genotype and posted to medical record.
Sample for CYP2D6 Genotype Obtained: 9/22/2011
PG4KDS CYP2D6 Genotype Result: (*4/*4)2N

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.

This result signifies that the patient has two copies of a non-functional 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
Jane Smith, Pharm.D., pager 1234
(*)4/*4)2N  AUTOMATIC  Abnormal Priority  PM  CYP2D6 - Poor Metabolizer  1C, 2GG, 3U, 4R, 5CCC, 6GGG
400 PG4KDS pharmacogenetic consults released to EMR to date
~10% are priority consults
Priority Results are Posted to Problem List

<table>
<thead>
<tr>
<th>Result in EMR</th>
<th>Consult Type</th>
<th>EMR Flag (Color)</th>
<th>Consult Priority</th>
<th>Phenotype</th>
<th>EMR Problem List Entry</th>
<th>Modular Section Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>(*4/*4)2N</td>
<td>Automatic</td>
<td>Abnormal</td>
<td>Priority</td>
<td>PM</td>
<td>CYP2D6 - Poor Metabolizer</td>
<td>1C, 2GG, 3U, 4R, 5CCC, 6GGG</td>
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If a clinician selects a medication that is linked to the pharmacogenomic alert (e.g. codeine & CYP2D6), a Warning Box will appear with a brief description of the potential problem. The clinician is then directed to select an appropriate action before proceeding.
Pharmacist Education
On-Site Pharmacist Education

- ACPE seminars
- Self-paced competencies
Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (CYP2C19) Genotype and Clopidogrel Therapy

SA Scott¹, K Sangkuhl², EE Gardner³, CM Stein⁴,⁵, J-S Hulot⁶,⁷, JA Johnson⁸,⁹,¹⁰, DM Roden¹¹,¹², TE Klein² and AR Shuldiner¹³,¹⁴

Clin Pharmacol Ther. 2011, 90:328-32

Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 Genotypes and Warfarin Dosing

JA Johnson¹, L Gong², M Whirl-Carrillo³, BF Gage³, SA Scott⁴, CM Stein⁵, JL Anderson⁶, SE Kimmel⁷,⁸,⁹, MTM Lee¹⁰, M Pirmohamed¹¹, M Wadelius¹², TE Klein² and RB Altman²,¹³


CPIC guidelines freely available on pharmgkb.org
Patient Education
Dear __________,

During your/your child’s treatment at St. Jude Children’s Research Hospital, you chose to participate in the PGEN4Kids study (PG4KDS). As a part of this study, a test was performed to look for variations in certain genes. A gene refers to a part of the DNA, and variations in genes may affect how well you/your child respond to or whether you/your child have side effects from specific medicines.

You agreed to have hundreds of your/your child’s genes tested for variations. Over time, scientists are discovering which of these gene tests are important enough to add to your/your child’s medical record. Once a gene test is added to the medical record, doctors and other caregivers can see the results and use the information when prescribing medicines for you/your child. Each time a gene test result is placed into your/your child’s St. Jude Children’s Research Hospital medical record, you chose to receive a letter notifying you of the result. Because your genes stay the same even as you age, the results may affect how doctors prescribe medicines for you/your child over your whole lifetime. You may want to share this information with your/your child’s other doctors outside of St. Jude, who may not have easy access to all of the information in the St. Jude medical record.

You are receiving this letter to inform you that the cytochrome P450 2D6 (CYP2D6) gene test was recently moved into your/your child’s medical record. **Based on your results, you are predicted to be an extensive metabolizer. This means you have normal CYP2D6 enzyme activity. You have the same gene status as most other people; about 78% of people are extensive metabolizers, as shown in the chart below.**

CYP2D6 metabolizes many different medicines, including codeine and some other pain relief medicines, some antidepressants and other psychiatric medicines, and beta blockers (used for heart conditions and high blood pressure). **Your/your child’s CYP2D6 gene test result suggests that for most medicines there is no reason to selectively adjust the dose of medicines metabolized by CYP2D6 enzymes.** For information on how to understand your/your child’s
Cytochrome P450 2D6 (CYP2D6) and medicines

When you take a medicine (drug), your body has to have a way to handle the medicine. One way is for enzymes to metabolize (break down) the medicine. A family of enzymes called cytochrome P450s have the ability to break down certain medicines. By metabolizing a medicine, cytochrome P450 enzymes make the medicine either more or less active, depending upon the medicine. Cytochrome P450 2D6 (CYP2D6) is part of the cytochrome P450 family of proteins in the body. It is responsible for breaking down many medicines that are commonly used.

Pharmacogenetic testing

DNA is like a set of instructions for your body that can help decide how well your enzymes will work. Each person differs from another at the DNA (gene) level. This means that each person has small differences in the genes that code for enzymes. The part of DNA that instructs how well the CYP2D6 enzyme will work is
Conclusions

• Prospective pharmacogenomic testing in patients with a high likelihood of receiving drugs of interest can identify patients at high risk for toxicity or lack of benefit.

• Pharmacogenomic consults, coupled with clinical decision support alerts, are integral for clinical implementation of pharmacogenomics.
The PGEN4Kids Team

Clinical Pharmacists

Database Managers

PI: Mary V. Relling, PharmD

Clinical Laboratory Staff

St. Jude Children's Research Hospital

AACP Annual Meeting