Pharmacogenomics Research Network (PGRN) programs related to genomic medicine implementation: CPIC, TPP, eMERGE-PGx

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Vanderbilt University School of Medicine
Two faces of pharmacogenetics

Serious ADRs

Variability in efficacy

Pharmacogenomics Research Network

Δ diastolic BP with HCTZ (AA population)
PharmGKB is a comprehensive resource that curates knowledge about the impact of genetic variation on drug response for clinicians and researchers.

Search PharmGKB:

CYP2C8 substrates

<table>
<thead>
<tr>
<th>Drug Name</th>
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<td>Paclitaxel</td>
<td>Solid Tumors</td>
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<tr>
<td>Cerivastatin</td>
<td>Hyperlipidemia</td>
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</table>

How would CYP2C8 variants affect disposition and response to antidiabetic agents?

Find out more

CYP2C8 VIP Summary

UGT1A1 VIP summary

Venlafaxine PK Pathway

CPIC TCAs/CYP2D6 and CYP2C19

PharmGKB Knowledge Pyramid

Clinically-Relevant PGx

- Well-known PGx associations
- Clinically relevant PGx summaries
- PGx drug dosing guidelines
- Drug labels with PGx info
- Genetic tests for PGx
- Star (*) allele translations

PGx-Based Drug Dosing Guidelines

- CYP2C19 and CYP2D6/amitriptyline and nortriptyline:
  - article and supplement
- HLA-B/allopurinol:
  - article and supplement
- more guidelines...

PGx Research

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

CPIC Gene-Drug Pairs

TPP Gene Tables
The implementation vision

- The Vanderbilt PREDICT program
- The Clinical Pharmacogenomics Implementation Consortium
- The Translational Pharmacogenomics Program in PGRN
- The eMERGE-PGx project

"Here's my sequence..."

New Yorker, 2000
1. Select populations of patients who are “at high risk” for receiving a drug with an actionable “pharmacogenetic” story.

2. Genotype all of them on a platform that assays genotypes important for variable actions of many drugs preemptively.

3. Store the genotypes, develop the informatics tools to provide point-of-care advice. Track outcomes. The “easy stuff”.

**PREDICT**

Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment
Clopidogrel label revision March 2010 identifies a high risk group
CYP2C19 genotypes in 12,521 PREDICT patients (9/2010-4/2013)

- 2.7% homozygous
- 18.9% heterozygous
- 12.2% non-actionable variant
- 66.1% no common variant
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<th>Gene Result</th>
<th>Number of Patients</th>
<th>% of Total Patients</th>
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<tr>
<td>Total</td>
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<tr>
<td>Total</td>
<td></td>
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<td>2,703</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

Grand Total  |                      |                   | 2,703              | 100.00%             |
Clopidogrel Poor Metabolizer Rules

Genetic testing has been performed and indicates this patient may be at risk for inadequate anti-platelet response to clopidogrel (Plavix®) therapy.

This patient has been tested for CYP2C19 variants, and has identified the presence of two copies of a risk allele which is associated with poor metabolism of clopidogrel. Poor metabolizers treated with clopidogrel at normal doses exhibit higher rates of stent thrombosis/other cardiovascular events.

(See StarPanel for patient-specific CYP2C19 gene result.)

Treatment modification is recommended if not otherwise contraindicated:
Click here for more information

- Prescribe prasugrel (EFFIENT) 60 mg x 1 dose now, followed by 10mg daily to start at 10am tomorrow
- Prescribe ticagrelor (BRILINTA) 180 mg x1 dose now, followed by 90 mg twice daily to start at 10am tomorrow

If prasugrel (EFFIENT) or ticagrelor (BRILINTA) are not selected, please choose desired action:
Click here for more information

- Maintain requested daily dose of clopidogrel (PLAVIX)
  75 mg Daily, start 10am

Select medication route: PO

NOTE: The Vanderbilt F&T Committee recommends that prasugrel or ticagrelor replace clopidogrel for poor metabolizers unless contraindicated, if feasible. If this is not possible maintain standard dose of clopidogrel. The guidelines above were developed based on outcome studies of patients who received a stent into a coronary artery.
Phenotype: POOR METABOLIZER

Treatment recommendation for this patient:

Problem: This patient's CYP2C19 genotype is associated with very impaired metabolic activation of the prodrug clopidogrel (Plavix) and impaired response to clopidogrel.

Reasons: In patients with ACS or who undergo PCI, reduced clopidogrel activation in this genotype results in significantly reduced active metabolite levels, reduced platelet inhibition, increased residual platelet aggregation, and decreased clinical efficacy (elevated risk for recurrent major cardiovascular events, including stent thrombosis).

Recommendations:
MODIFY TREATMENT BY CHOOSING ONE OF THE FOLLOWING:
Prescribe:
Prasugrel (EFFIENT) 60 mg loading dose followed by 10 mg daily
or
Ticagrelor (BRILINTA) 180 mg loading dose followed by 90 mg twice daily
First data peek...

- 7405 PREDICT genotyped patients from 10/1/2010 to 6/30/2012:
  - 1620 with stent placed
  - “final” antiplatelet therapy identified at 90 days

![Proportion prescribed drug within genotype group](chart)

- **Poor Metabolizer**
  - Clopidogrel: 53%
  - Prasugrel: 47%
  - Ticagrelor: 0.0%
  - N=32

- **Intermediate Metabolizer**
  - Clopidogrel: 79%
  - Prasugrel: 21%
  - Ticagrelor: 0.0%
  - N=305

- **Indeterminate**
  - Clopidogrel: 93%
  - Prasugrel: 6%
  - Ticagrelor: 0.8%
  - N=122

- **Normal**
  - Clopidogrel: 94%
  - Prasugrel: 6%
  - Ticagrelor: 0.4%
  - N=1079

“Final” therapy

- Clopidogrel
- Prasugrel
- Ticagrelor
**General Information:** (12/05/12 09:05, Teresa)
- PCP: 
- Card: 
- Arrhythmia/Device: Dr. Dan Roden, VUMC

**Structured Problems:** (12/05/12 09:05, Teresa)
- Coronary artery disease
- Aortic valve stenosis
- Congestive heart failure
- Mitral valve regurgitation
- Chronic atrial fibrillation
- Hypertension
- Hyperlipidemia
- Gastroesophageal reflux disease
- Chronic Renal insufficiency
- Paroxysmal ventricular tachycardia
- s/p VTach cardiac arrest, 6/12/09
- ICD Shock for VTach, 9/14/2010
- Hx Blood Transfusion
- Anesthesia Difficulties:
- Dental Hygiene:
- Emergency #:

**Significant Procedures:** (12/05/12 09:05, Teresa)

- Adverse and Allergic Drug Reactions: (02/21/13 12:25)
  - Aldactone (rash)

- Drug Genome Interactions: (01/05/13 13:03)
  - clopidogrel sensitivity: NORMAL METABOLIZER - gene: CYP2C19 - gene result: *1/*1
  - warfarin sensitivity: Hyper Responder - gene results: VKORC1 G/G; CYP2C9 *1/*3
  - simvastatin sensitivity: HIGH MYOPATHY RISK, MINOR ALLELE HOMOZYGOUS (C,C) - gene: SLC01B1 - gene result: *5/*5
  - thiorurine sensitivity: INTERMEDIATE MYELOTOXICITY RISK, MINOR ALLELE HETEROZYGOUS - gene: TPMT - gene result: *1/*3c
  - tacrolimus sensitivity: HYPO RESPONDER - gene: CYP3A5 - gene result: *1/*3

- Note: Most genetic variants with therapeutic considerations demonstrate reproducibility of greater than 98%. Please visit [www.mydruggenome.org](http://www.mydruggenome.org) for additional information.

- Medications: prepare to print print and give pt. Show Hx of medications
  - Drug/Herb Interactions (02/21/13 12:25)
  - simvastatin (zocor) 20 mg orally nightly
  - Quinapril (accupril) 40 mg orally daily
  - Zolpidem (ambien) 10mg orally daily
  - Carvedilol (coreg) 6.5 mg orally twice daily with meals
  - Furosemide (lasix) 20 mg 3 tablets orally daily
  - Digoxin (lanoxin) 0.125 mg 1/2 tablet orally daily
  - **Warfarin (coumadin)** 2 mg, 2 tablets on sun by mouth and 1 1/2 tablet on other days
  - Potassium (k-dur) 10meq 3 tablets orally daily
Multiplexed testing for pharmacogenetic variants
(after 5 drug-gene pairs...)

Total n=12,451
(9/10-4/13)

- 0 variants (11.8%)
- 1 variant (29.6%)
- 2 variants (31.8%)
- 3 variants (18.4%)
- 4 variants (6.6%)
- ≥5 variants (1.9%)
Another group at “high risk”
A case for preemptive genotyping

In a cohort of 53,196 “Medical Home” patients followed for up to 5 years, how many received one of 58 drug(s) that include PGx information in their FDA label?

65% received ≥1 med within 5 years
Prognostic Model Ordering CDS
St. Jude patients frequently receive 33 high risk drugs

- In 2011, 2023 of 4245 patients (48%) who received medications at St. Jude received orders for at least one of 33 “high-risk” drugs.
- Over 18% of patients received codeine or tramadol
  - 12% of these patients can be expected to have high-risk diplotypes and therefore require alternative agents
TPMT Pre-pharmacogenetic test warning: at point of care to prescriber

TPMT genotype data is recommended before using a thiopurine (mercaptopurine, thioguanine, and azathioprine). A TPMT genotype test result does not appear to be available for this patient. Please considering ordering a TPMT genotype test to help guide prescribing.

Add Order for:

[ ] TPMT Genotype → T:N, Collect Now, Blood, ONCE
*WARNING*

This patient has an active entry on the problem list CYP2D6 ULTRA-RAPID METABOLIZER. Ultra-rapid metabolizers of codeine are expected to experience a higher incidence of side effects from codeine than normal. Other pain medicines or cough suppressants should be considered. Please consult a clinical pharmacist or review the clinical pharmacy consult note related to this problem.

Alert Action
- Cancel entry
- Continue w/order
- modify entry
CPIC’s framework: if you had the genotype result, how should you act on it?

- > 60 Clinicians, scientists
- 33 institutions
- 12 countries
- Observers: NIH and FDA
PGRN Translational Pharmacogenetics Project (TPP)

- **Goal**: Implement CPIC guidelines into diverse real-world clinical settings
  - Harness the multidisciplinary expertise of the PGRN to implement routine ‘actionable’ pharmacogenetic based dosing and drug selection within diverse health care systems.

......the “Science of Translation”
PGRN Translational Pharmacogenomics Project (TPP): Translating CPIC Guidelines into Clinical Practice

- **Aim 1**: Accelerate writing/publication of CPIC guidelines
- **Aim 2**: Implementation of CLIA-approved evidence-based pgx tests for patient care.
  - Egs., *TPMT*/thiopurines; *CYP2C19*/clopidogrel; *CYP2C9, CYP4F2* and *VKORC1*/warfarin; DMET/preemptive testing; custom panels
  - Report results in EHR/develop clinical decision support tools
  - Track implementation metrics (test adoption rates, test turnaround times, test results, genotype failure rates, and the number of prescription modifications)
- **Aim 3**: Develop and implement methodologies and standardized formats to report results to prescribers
  - Identify common logistical barriers and develop a “tool-box” of solutions
- **Aim 4**: Facilitate adoption of pgx; disseminate information
Aim 1: CPIC Guidelines/Updates

- **Overview of CPIC** (Relling and Klein, Clin Pharmacol Ther. 2011;89(3):464-7)
- **TPMT/Thiopurines** (Relling et al., Clin Pharmacol Ther. 2011;89(3):387-91)
- **CYP2C19/Clopidogrel** (Scott et al., Clin Pharmacol Ther. 2011;90(2):328-32)
- **CYP2C9-VKORC1/Warfarin** (Johnson et al., Clin Pharmacol Ther. 2011;90(4):625-9)
- **HLA-B/Abacavir** (Martin et al., Clin Pharmacol Ther. 2012; 91(4):734-8)
- **SLCO1B1/simvastatin** (Wilke et al., Clin Pharmacol Ther. 2012;92:112-7)
- **HLA-B/carbamazepine** (Leckband et al., submitted)
- **Updates** (TPMT/Thiopurines, in press; CYP2C19/clopidogrel, in press)
- **Others in progress:**
  - DPYD-5FU/capecitabine, HLA-B/phenytoin, G6PD/rasburicase, Septra, UGT1A1/irinotecan, IL28B/peginteron, CTFR/Ivacaftor, CYP2D6/SSRIs
CPIC Guidelines
Immediate future plans

• New CPIC Guidelines in Progress or Planned
  • DPYD-5FU/capecitabine
  • HLA-B/phenytoin
  • G6PD/rasburicase, Septra
  • UGT1A1/irrenotecan
  • IL28B/peginteron
  • CTFR/Ivacaftor
  • CYP2D6/SSRIs
• Updates (6)
• Improved linkage between CPIC guidelines and TPP tools
Aim 2: Implementation

- **CYP2C19/clopidogrel - all sites**
- **Others (1 or more sites)**
  - TPMT-azathioprine, thioguanine, mercaptopurin
  - HLA-B*5701-Abacavir
  - HLA-B*1502-Carbamazepine
  - IL28B-Ribavirin-Pegylated Interferon
  - CYP2D6-codeine, amitriptyline, tramadol, fluoxetine, paroxetine, ondansetron
  - SLCO1B1-simvastatin
  - CYP2C9/VKORC1-CYP2C9

- **Models**
  - Targeted rapid turn-around
    - Single gene (UMD, Mayo)
  - Pre-emptive
    - Multiplex
      - DMET/ADME platform (VU, St. Jude, OSU)
      - Custom panels (UFI)
Aim 2: Implement PGx

University of Florida

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St. Jude (PAAR4Kids)

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Vanderbilt

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# Tracking Implementation Metrics

## Pharmacogenetic (Pgx) Testing Adoption
- Platform (e.g., Illumina ADME Chip, Affy DMET Array, Taqman, etc.)
- Genes
- Target populations
- Testing volume (cumulative total; by month)
- Test ordered and mode of order entry (e.g., Computerized Physician Order Entry, EMR, Paper, Automated rule)
- Role of provider ordering the test
- Practice setting where the order originated (e.g., inpatient, outpatient)
- Cost of testing
- Number of tests ordered but not completed
- Other lab QA measures: genotype failure rates, call rates, concordance, test turnaround time
- Pharmacogenetic test adoption rates for a prospective or anticipatory model
- Pharmacogenetic test adoption rates for a prescription and indication specific model

## Pharmacogenetic Test Results
- Timing of result: Median time between Pgx order and Pgx report to prescribers
  - Median time between Pgx result and new or revised target drug order
- Genotype distribution by haplotype
- Proportion of tested patients with actionable genotypes (meet criteria for consult or CDS)

## Pgx Consultation and Clinical Decision Support (CDS)
- Number of Pre-emptive tests (Automated trigger vs. Provider requested / On-demand)
- Automated clinical decision support delivery vehicle (e-prescribing / CPOE / EMR), method [active (interruptive)/passive)], recommendation, and user response
- Manual clinical decision support delivery – role, communication mode, successful contact w/ primary decision maker, response

## Provider Genotype-Guided Prescription Metrics
- Proportion of patients with Pgx Consultation/CDS leading to a new or revised prescription for target drug
- Time between Pgx result and new or revised target drug order

## Adherence to CPIC Pharmacogenomic Guidelines
- Adherence to recommendation based on genotype
- Reasons for non-adherence

## Communication of Pharmacogenomic Information to Patients
- Role of provider communicating results
- Mode of communication (documented verbal discussion, messaging)
Lessons Being Learned

• More complicated than one might think
  • Engagement of many parties within the healthcare system especially “clinician champions”
• Strong institutional support
• Need for active clinical decision support that interactively interprets genetic data and guides providers through prescription options
• Recurrent education/in-service programs
• Iterative process:
  • Monitoring uptake of pharmacogenomic testing and genotype-tailored prescriptions as an early signal for implementation barriers that need to be addressed.
Aim 3: Develop standardized formats to report results to prescribers

- Results summary/TPP metrics tables
- Diplotype-phenotype and CDS “Look-up Tables”
  - CYP2C19
  - CYP2D6
  - TPMT

http://www.pharmgkb.org/page/tppTables
Aim 4: Dissemination

Pharmacogenomics Research Network

Operation: Overcoming Challenges of Real-World Implementation

The Pharmacogenomics Research Network Translational Pharmacogenomics Program:

The promise of "personalized" pharmacotherapy in an individualized health care setting, resulting in improved patient care, is a fundamental tenet of medical practice. However, achieving this promise requires not only the development of novel technologies and methodologies but also the effective dissemination of knowledge to the broader healthcare community.

The Pharmacogenomics Research Network (PGRN) Translational Pharmacogenomics Program seeks to identify barriers and develop real-world solutions to implementation of evidence-based pharmacogenomic tests in diverse health care settings. Dissemination of the resulting tool kit of "implementation best practices" will be valuable to a broad audience.

Despite a number of important pharmacogenomic discoveries, substantial evidence supporting clinical utility, and US Food and Drug Administration labels recommending use of pharmacogenetic testing, few pharmacogenetic tests have made their way into routine clinical practice. Barriers to adoption of pharmacogenetic tests in practice are substantial and include (i) logistical issues of implementing accurate and rapid turnaround genotyping in a Clinical Laboratory Improvement Amendments-approved laboratory setting; (ii) lack of a standardized format for the return of test results into the electronic health record; (iii) lack of prospective genotype-directed pharmacologic randomized controlled trials validating treatment algorithms; (iv) lack of clear recommendations for pharmacogenetic testing by professional associations; (v) lack of infrastructure to provide decision support for genomic medicine; and (vi) cost considerations and reimbursement.

One barrier to clinical implementation addressed by the PGRN is the lack of clear, curated, peer-reviewed pharmacogenomic guidelines that translate laboratory test results into actionable prescribing decisions for specific drug–gene pairs. The PGRN Clinical Pharmacogenomics Implementation Consortium (CPIC) is a shared initiative between the Pharmacogenomics Knowledgebase (PharmGKB) and the PGRN. The CPIC produces clinical guidelines that are drug–gene pair specific, peer-reviewed, published, and posted to PharmGKB; the guidelines specifically do not consider how or why the genotype data were obtained but instead how to act on genotype data that have been obtained. CPIC guidelines contain information needed for clinical implementation, including tables that summarize the relevant functional gene variants and probable phenotypes, and recommendations regarding drug dosing or drug choice based on phenotype (http://www.pharmgkb.org/page/cpic). All CPIC recommendations are extensively annotated and supported by evidence; in addition, the strength of the recommendations is indicated. The guidelines are freely available at PharmGKB (http://www.pharmgkb.org/page/cpicGeneDosePair), are updated on a regular basis, and are not linked to any commercial services, genotyping platforms, or financial interests. CPIC guidelines published to date include:

- Genotype: effective Customized typing Array
- Salzler A, TE Klein and RB Altman

There have been astounding advances in genotyping and sequencing technologies in the past decade. For example, Life Technologies recently announced the introduction of a sequencing technology that can sequence the entire human genome for less than $1,000. Based on these advances, it is likely that increasing amounts of patient-specific genomic information will be available, and that genetic information will therefore be available to clinicians preemptively and when it is needed. Such an approach obviates many of the current barriers described in Table 1 and moves the discussion away from "should I order the pharmacogenetic test" to "can I ignore use of pharmacogenetic information in this patient when I already have it?" Availability of large amounts of genetic information probably represents the future, and generation of larger amounts of genetic information for future use is more cost-effective than testing for one or one single-gene/1-polymerase SNP (SNP) at a time. As such, some institutions that are undertaking clinical implementation of pharmacogenomics are genotyping on a broader panel of SNPs so that most of the information will be available when needed.

The University of Florida and Stanford University were funded under a National Institutes of Health Clinical Translational Science Award administrative supplement to pilot (at the University of Florida) and replicate (at Stanford) a clinical pharmacogenetics implementation. We are initially targeting clopidogrel therapy and its association with CYP2C19 genotype, but we are genotyping a broader array of genetic variants so as to allow for future "when needed" use of pharmacogenetics information. Genotypes from the chip beyond CYP2C19 will be moved to the patient's medical record once the pharmacy and therapeutics committees at each participating hospital approves the implementation of the relevant drug–gene pair, regardless of whether the patient is actually taking the relevant drug at the time. This allows the genotypes to be available when the relevant drug is being considered for use in the patient.
eMERGE-PGRN Partnership

PGx capabilities:
• Array-based assay for pharmacogenes
• Drug-gene guidelines
• CLIA & QC standards

EMR-informatics capabilities
• Privacy
• Electronic phenotyping
• Large populations
The platform: PGRN-Seq

- 84 Very Important Pharmacogenes
- Nominated by the 14 PGRN sites
- Multiple rounds of balloting
- Each site was able to include ≥2 genes of its choosing
- Drug metabolism, transporters, targets
- Nimblegen custom capture array; coding UTRs + probes for each variant on Illumina and Affy ADME/DMET platforms
# Average SNVs per Individual

<table>
<thead>
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<th>Panel</th>
<th>Total SNVs</th>
<th>Novel SNVs</th>
<th>Unique SNVs</th>
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<td>Panel 1 - HapMap (n=64)</td>
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<td>33</td>
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<tr>
<td>Panel 2 - Golden (n=92) Thummel</td>
<td>1259</td>
<td>35</td>
<td>13</td>
</tr>
</tbody>
</table>
PGRN-Seq: Status/issues

- CYP2D6 problematic: many variants, pseudogene, phenotype of interest is the compound heterozygote; may also be an issue for other platforms
- HLA: May be able to interrogate specific variants of interest but unlikely to be able to resequence with current technology approach
- Comparison to Illumina ADME: 88/95 HapMap samples concordant at ~150 sites; one site accounts for discordance in 7 samples
Aim 1

Develop list of actionable variants (eMERGE, CPIC, ...)

Identify target patients

Resequence VIP genes; Identify actionable variants
eMERGE-PGx project

Aim 1

Develop list of actionable variants (eMERGE, CPIC, ...)

Identify target patients

Resequence VIP genes; Identify actionable variants

Aim 2

Actionable variants

EMR deposit

- Result display
- Decision support

Outcomes

- Performance metrics
- Healthcare impact

The eMERGE Network
electronic Medical Records & Genomics
PharmacoGenomics Research Network
Aim 1

Identify target patients

Resequence VIP genes; Identify actionable variants

Aim 2

Actionable variants

EMR deposit
- Result display
- Decision support
- Outcomes
- Performance metrics
- Healthcare impact

Aim 3

- Create repository of variants of unknown significance
- Initiate studies of function and of genotype-phenotype relationships

Aim 1

Develop list of actionable variants (eMERGE, CPIC, ...)

Identify actionable variants

Result display
- Decision support
- Outcomes
- Performance metrics
- Healthcare impact
## Targeted enrollment

<table>
<thead>
<tr>
<th>Study site</th>
<th>American Indian/Alaska Native</th>
<th>Asian</th>
<th>Native Hawaiian or Other Pacific Islander</th>
<th>Black or African American</th>
<th>White</th>
<th>Total (% of Females)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCHMC/CHB</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>54</td>
<td>438</td>
<td>500 (41)</td>
</tr>
<tr>
<td>CHOP</td>
<td>0</td>
<td>64</td>
<td>0</td>
<td>516</td>
<td>709</td>
<td>1289 (50)</td>
</tr>
<tr>
<td>Geisinger</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>24</td>
<td>768</td>
<td>800 (66)</td>
</tr>
<tr>
<td>GHC</td>
<td>16</td>
<td>23</td>
<td>1</td>
<td>35</td>
<td>825</td>
<td>900 (37)</td>
</tr>
<tr>
<td>Marshfield</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>750</td>
<td>750 (56)</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>960</td>
<td>1000 (50)</td>
</tr>
<tr>
<td>Mt. Sinai</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>486</td>
<td>414</td>
<td>900 (60)</td>
</tr>
<tr>
<td>Northwestern</td>
<td>3</td>
<td>44</td>
<td>0</td>
<td>191</td>
<td>512</td>
<td>750 (62)</td>
</tr>
<tr>
<td>Vanderbilt</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>100</td>
<td>893</td>
<td>1000 (52)</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>172</td>
<td>1</td>
<td>1426</td>
<td>6269</td>
<td>7889 (53)</td>
</tr>
</tbody>
</table>
## Initial target drugs

<table>
<thead>
<tr>
<th>Facility</th>
<th>Drugs and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NU</td>
<td>clopidogrel and warfarin have been approved Revisit simvastatin</td>
</tr>
<tr>
<td>Geisinger</td>
<td>Have not made a final decision, but likely simvastatin. Others are in planning stages.</td>
</tr>
<tr>
<td>GHC/UW</td>
<td>carbamazepine (other pairs implemented at the UW)</td>
</tr>
<tr>
<td>Mayo</td>
<td>abacavir, interferon, thiopurines, carbamazepine In planning: warfarin, clopidogrel, simvastatin</td>
</tr>
<tr>
<td>Vanderbilt</td>
<td>clopidogrel, warfarin, simvastatin in place. In planning: thiopurines</td>
</tr>
<tr>
<td>Marshfield</td>
<td>clopidogrel, warfarin, simvastatin</td>
</tr>
<tr>
<td>Mt. Sinai</td>
<td>clopidogrel, warfarin, simvastatin</td>
</tr>
<tr>
<td>CHOP</td>
<td>carbamazepine, thiopurines</td>
</tr>
<tr>
<td>BCH/CCMH</td>
<td>codeine</td>
</tr>
</tbody>
</table>
## Subject selection

<table>
<thead>
<tr>
<th>Institution</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>NU</td>
<td>Recruitment goal = 750 participants from internal medicine. Selected using a predictive algorithm (modified from Vanderbilt).</td>
</tr>
<tr>
<td>Geisinger</td>
<td>Have already applied the Vanderbilt algorithm (modified) to MyCode® population and identified candidates.</td>
</tr>
<tr>
<td>GHC/UW</td>
<td>900 subjects selected using a predictive algorithm (Vanderbilt). A subset of 450 will be selected for confirmatory testing and return of results, to include all those with an actionable finding per the PGx chip and the balance to be made up of randomly selected subjects who did not have an actionable finding.</td>
</tr>
<tr>
<td>Mayo</td>
<td>Modified VU algorithm as applied to our biobank. Invitations sent to 2000 individuals by 10/15/12. We expect to complete consent of 1000 subjects by 12/31/12.</td>
</tr>
<tr>
<td>Vanderbilt</td>
<td>Identified as likely to be prescribed the target medications (clopidogrel, warfarin, simvastatin) within next 3 years, trained on ~18,000 patients.</td>
</tr>
<tr>
<td>Marshfield</td>
<td>Best algorithm for preemptive testing: Over 50 with no prior Rx.</td>
</tr>
<tr>
<td>Mt. Sinai</td>
<td>Based on Vanderbilt’s algorithm for eMERGE-PGx.</td>
</tr>
<tr>
<td>CHOP</td>
<td>Adverse events database, asthma, ....</td>
</tr>
<tr>
<td>BCH/Cinn</td>
<td>Codeine/CYP2D6</td>
</tr>
</tbody>
</table>
Aim 1: Deploy the PGRN-Seq platform across eMERGE.
• > 3000 samples collected to date of 9500 total samples expected
• 1st 300 samples in process on PGRN-Seq at CIDR
• Expect ≥ 100 samples / site sequenced with variants called and displayed along with basic phenotypic information in a searchable database by end of 2013

Aim 2: Integrate validated genotypes into the EMR and assess uptake, acceptance, and clinical impact.
• Process outcomes measures to be collected across the network developed and being vetted at upcoming Steering Committee meeting

Aim 3: Analyze variants of unknown significance.
• Variant repository structure developed in conjunction with PGRN
• Important genotype / phenotype use cases may include:
  • CACNA1S        malignant hyperthermia
  • KCNH2             channelopathy/arrhythmia
  • LDLR                familial hypercholesterolemia
  • RYR1                malignant hyperthermia
  • RYR2                channelopathy/arrhythmia
  • SCN5A             channelopathy/arrhythmia
Extra slides...
2010-2013 Implementation Timeline
# Drugs Proposed for Implementation in eMERGE-PGx, by Site

<table>
<thead>
<tr>
<th>Site</th>
<th>abacavir</th>
<th>carbamazepine</th>
<th>clopidogrel</th>
<th>codine</th>
<th>interferon</th>
<th>montelukast</th>
<th>morphine</th>
<th>omeprazole</th>
<th>ranitidine</th>
<th>simvastatin</th>
<th>thio purines</th>
<th>warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CCHMC</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geisinger</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>GHC/UW</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marshfield</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayo</td>
<td>X</td>
<td>X</td>
<td>(X)</td>
<td></td>
<td>X</td>
<td>(X)</td>
<td></td>
<td></td>
<td>(X)</td>
<td>X</td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td>Mount Sinai</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NU</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td>(X)</td>
<td></td>
<td></td>
<td>(X)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vanderbilt</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(X) = planned
Personalized DAPT - CYP2C19 - UMMC Workflow
(5-hour turnaround)

Patient
- LHC indicated
  - Potential indication for dual anti-platelet therapy based on indication for LHC
  - Final Therapy Choice Provided

Cardiology Team
- Agree to TPP inclusion
- IM or PM - Alternative Therapy Considered
- Cardiology Fellow orders Drug of Choice

Research Coordinator
- Eligibility confirmed
- Consent Obtained

Cath Lab Team
- CYP2C19 genotype ordered in PowerChart
- LHC performed
- 6 cc blood collected

UMMC Pathology
- Delivered by RC
- Sample accessioned
- Genotype result entered into Cerner
- Results called from Call Center to Cardiology Fellow or IC

TGL
- Picked up by TGL
- Genotype Completed
- Result Faxed
Personalized DAPT - CYP2C19 Baltimore VAMC Workflow (5-hour turnaround)

**Patient**
- LHC indicated
- Potential indication for dual anti-platelet therapy based on indication for LHC
- Final Therapy Choice Provided

**Blue Team**
- Referred for LHC & TPP inclusion
- If POOR or INTERMEDIATE Metabolizer, Critical Alert Call from Path Lab to Blue Fellow
- Alternative Therapy Considered
- Blue Fellow orders Non-Formulary Med Consult

**Research Coordinator**
- Eligibility confirmed
- Consent Obtained
- CPRS genotype order entered
- RC enters Clinical Warning in CPRS
- Call or Page Clinical Pharmacist
- Pharmacist Reviews NF Medication order

**Cath Lab Team**
- LHC performed
- 6 cc blood collected
- Delivered by RC

**Pathology Lab Team**
- Sample processed
- Genotype Result Entered into CPRS
- Picked up by TGL
- Result Faxed

**TGL**
- Genotype Completed
Proposal: Year 03-04 Continuation:
Aims 3 and 4: Develop standardized formats to report results; facilitate adoption of pgx through dissemination

- Diplotype-phenotype and CDS “Look-up Tables” and templates suitable for uploading in EHRs (EPIC, Cerner)
  - Companions to all CPIC guidelines
- Implement “Look up” templates at TPP implementation sites
- Dissemination
  - Make “Look-up” and TPP implementation table templates available for downloading on PharmGKB ([http://www.pharmgkb.org/page/tppTables](http://www.pharmgkb.org/page/tppTables))
- TPP and individual group publications
- Education tools
## Examples of pharmacogenetically high-risk drugs used in 2011 at St Jude

<table>
<thead>
<tr>
<th>Affected drugs</th>
<th>Number of pts receiving drug</th>
<th>Number of orders</th>
<th>Relevant gene</th>
<th>% of pts with high-risk diplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine/tramadol</td>
<td>779</td>
<td>3011</td>
<td>CYP2D6</td>
<td>12%</td>
</tr>
<tr>
<td>Thiopurines</td>
<td>317</td>
<td>6223</td>
<td>TPMT</td>
<td>9%</td>
</tr>
<tr>
<td>Fluoropyrimidines</td>
<td>12</td>
<td>154</td>
<td>DPYD</td>
<td>2%</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>793</td>
<td>5571</td>
<td>G6PD</td>
<td>5%</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>51</td>
<td>294</td>
<td>CYP2D6</td>
<td>12%</td>
</tr>
</tbody>
</table>
St. Jude patients frequently receive these 33 high risk drugs

• In 2011, 2023 of 4245 patients (48%) who received medications at St. Jude received orders for at least one of 33 “high-risk” drugs.

• Over 18% of our patients received codeine or tramadol
  • 12% of these patients can be expected to have high-risk diplotype and therefore require alternative agents
# Pharmacogenetics Implementation Status

<table>
<thead>
<tr>
<th>Drug</th>
<th>Thiopurines</th>
<th>Codeine</th>
<th>Tramadol</th>
<th>Amitriptyline</th>
<th>Fluoxetine</th>
<th>Paroxetine</th>
<th>Abacavir</th>
<th>Simvastatin</th>
<th>Fluorouracil</th>
<th>Irinotecan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>TPMT</td>
<td>CYP2D6</td>
<td>CYP2D6</td>
<td>CYP2D6</td>
<td>CYP2D6</td>
<td>CYP2D6</td>
<td>HLA-B*5701</td>
<td>SLCO1B1</td>
<td>DPYD</td>
<td>UGT1A1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Outcomes</th>
<th>Myelosuppression</th>
<th>Increased toxicity or therapeutic failure</th>
<th>Increased toxicity or therapeutic failure</th>
<th>Increased toxicity or therapeutic failure</th>
<th>Increased toxicity or therapeutic failure</th>
<th>Hyper-sensitivity</th>
<th>Myopathy</th>
<th>Neutropenia</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Implementation Status</th>
<th>Live</th>
<th>Live</th>
<th>Live</th>
<th>Live</th>
<th>Live</th>
<th>Live</th>
<th>Live</th>
<th>Dec-12</th>
<th>Live</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>PG4KDS</td>
<td>Clinical</td>
<td>PG4KDS</td>
<td>PG4KDS</td>
<td>PG4KDS</td>
<td>PG4KDS</td>
<td>Clinical</td>
<td>PG4KDS</td>
<td></td>
</tr>
</tbody>
</table>

| Clinical impact of negative outcomes significant | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Scientific evidence for drug gene effect | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Patient target identifiable before they receive drug | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Alternative therapy available | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Gene added to DMET tracker | -- | ✓ | -- | ✓ | ✓ | ✓ | ✓ | -- | ✓ |
| Gene specific look up tables created | -- | ✓ | -- | ✓ | ✓ | ✓ | ✓ | -- | ✓ |
| Consult template written | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | -- | ✓ |
| Consult database updated | -- | ✓ | -- | ✓ | ✓ | ✓ | ✓ | -- | ✓ |
| CDS language developed | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Patient letters | -- | ✓ | -- | ✓ | ✓ | ✓ | ✓ | -- | ✓ |
| Gene specific "Do you Know..." sheet | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Patient medication card | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| PGEN formulary table updated | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Drug monograph updated in formulary | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| St Jude PG4KDS webpage updated | -- | ✓ | -- | ✓ | ✓ | ✓ | ✓ | -- | ✓ |
| Staff education | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Competencies | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| P & T Communication | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| POC Communication | -- | ✓ | -- | ✓ | ✓ | ✓ | ✓ | -- | ✓ |

**MEDICAL CENTER**

|--------------|----------|-----------|----------|-----------|----------|-----------|-----------|-----------|------------|

**Go-Live Date:**
1/7/2010
5/18/2011
11/7/2007
5/18/2011
2/10/2012
5/30/2012
5/30/2012
5/30/2012
10/11/2012
Personalized Medication Treatment

Each person responds differently to medicines. Your genes play a role in how you respond to medicines. Based on your history, your provider has ordered a test to learn more about which drugs are right for you. Having this information can help predict and prevent bad drug side effects.

Medication  Does your genetic test result affect your response to medications?

| Clopidogrel/Plavix® | Yes |
| Simvastatin/Zocor® | Yes |

The Clopidogrel Test

Clopidogrel (sounds like “kloh-PID-oh-grel”) is a blood thinner used to prevent clots that can cause a heart attack or stroke. Your genes can affect how well the drug works. This genetic test identifies how well you may respond to clopidogrel.

Your Risk

Sometimes clopidogrel does not prevent harmful strokes or clots as well as it should because of your genes. Your provider, often with the results of a lab test, can determine if clopidogrel is the right medicine for you.

The results of your test show that you have two versions of the gene that may put you at increased risk for this negative outcome.