Prospective Pharmacogenetic Testing in Practice: Vanderbilt PREDICT program and eMERGE-PGx

Josh Denny, MD, MS
1/29/12
The vision

"Here's my sequence…"

New Yorker, 2000
How will this vision actually start to be tested and become reality?

"Here's my sequence..."

New Yorker, 2000

Biomedical research

Commitment to information technology

Harnessing the healthcare system for discovery

Ability to nimbly adapt a healthcare system to evolving evidence
<table>
<thead>
<tr>
<th>Time Period</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-2003</td>
<td>Human Genome Project</td>
</tr>
<tr>
<td>2004-2010</td>
<td>Understanding the biology of genomes</td>
</tr>
<tr>
<td>2011-2020</td>
<td>eMERGE-PGx</td>
</tr>
<tr>
<td>Beyond 2020</td>
<td>Improving the effectiveness of healthcare</td>
</tr>
</tbody>
</table>
Table of Pharmacogenomic Biomarkers in Drug Labels

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labels may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

The table below lists **FDA-approved drugs with pharmacogenomic information in their labels**. Some, but not all, of the labels include specific actions to be taken based on genetic information. Relevant sections of the

n=83 (germline)
A case for preemptive genotyping & development of an “at risk” algorithm

In a cohort of 53,196 “Medical Home” patients followed for up to 5 years, how many received drug(s) that have a recognized pharmacogenetic “story”? 65% received ≥1 med within 5 years

Number of Patients

<table>
<thead>
<tr>
<th>Number of PGx Meds</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9525</td>
</tr>
<tr>
<td>2</td>
<td>8247</td>
</tr>
<tr>
<td>3</td>
<td>6833</td>
</tr>
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<td>4</td>
<td>5244</td>
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<td>5</td>
<td>3883</td>
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<td>6</td>
<td>2870</td>
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<td>7</td>
<td>2067</td>
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<td>8</td>
<td>1454</td>
</tr>
<tr>
<td>9</td>
<td>930</td>
</tr>
<tr>
<td>10+</td>
<td>1786</td>
</tr>
</tbody>
</table>

Schildcrout et al., CPT 2012
**Why Prospective? Risk of Side Effects highest at drug start**

- Medication initiation: warfarin
  - 1 month
  - 3 months
  - 6 months
  - 9 months
  - 12 months

- Medication initiation: simvastatin
  - 1 month
  - 3 months
  - 6 months
  - 9 months
  - 12 months

- Medication initiation: azathioprine
  - 1 month
  - 3 months
  - 6 months
  - 9 months
  - 12 months

- Medication initiation: tacrolimus
  - 1 month
  - 3 months
  - 6 months
  - 9 months
  - 12 months

- Medication initiation: abacavir
  - 1 month
  - 3 months
  - 6 months
  - 9 months
  - 12 months

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2. The SEARCH Collaborative Group, NEJM 2008
3. Higgs et al, Pharmacogenomics 2010
5. Mallal et al, NEJM 2008
PREDICT: Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment

- Multiplexed genotyping with Illumina ADME chip
- Prospective identification of those at risk to receive candidate medications
- Coupled with EMR-based Decision Support
- Work with Pharmacy & Therapeutics committee
Vanderbilt Population
410,000

Target Clinics
90,000

Prognostic Flag for Testing
24,000

Prognostic Testing
5,000

Reactive/Indication Testing
5,000

Genotyped for PREDICT
10,000

CLOPIDOGREL
SIMVASTATIN
WARFARIN
THIOPURINES

Clopidogrel Advisor
22%

Simvastatin Advisor
25%

Warfarin Advisor
100%

Thiopurine Advisor
3%
Prospective Genotyping
Using the Prognostic Model

• Model identifies patients who are highest risk for starting \textit{warfarin, clopidogrel, or simvastatin} therapy within the next three years as candidates for preemptive genotyping

• Used medical home population not on a target med previously (N~18000)

• Factors include:
  – Age, gender, race, and BMI when height is available (or weight when BMI is not available)
  – History of...Diabetes, coronary disease, atrial fibrillation, hypertension, atherosclerosis, congestive heart failure, previous DVT/PE, and end stage renal disease
Patient comes in, selected for genotyping (cardiac cath, predictive algorithm, etc)

184 variants

Genotype DB

Select variants put into EMR
- Validated
- CDS
- P&T review

Drop variants that don’t work well

~130 other variants validated of unknown significance

New research for drug-genome interaction discovery
P&T Committee
PREDICT research team
PharmacoGenomics Research Network

Patient-specific guidelines

Structured Problems:
- Coronary artery disease
- Aortic valve stenosis (severe)
- 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:
- Emergent:

Adverse and Allergic Drug Reactions:
- Allopurinol
- Drug Genome Interactions:
  - Normal Metabolizer
  - VKORC1 G/G
  - CYP2C9 *1/*3
  - Simvastatin sensitivity: HIGH MYOPATHY RISK, MINOR ALLELE HOMOZYGOS (C/C) - gene: SLC01B1 - gene result: *5/*5
  - Thiopurine sensitivity: INTERMEDIATE MYELOTOXICITY RISK, MINOR ALLELE HETEROZYGOS - gene: TPF1 - gene result: *1/*3c

Medications:
- Simvastatin (20mg) daily
- Quinapril (40mg) daily
- Zoledron (4mg) daily
- Carvedilol (50mg) daily
- Furosemide (20mg) daily
- Disopyramide (0.125mg) daily

Warfarin (coumadin) 2mg PO daily
- Potassium (20mg) daily
- Amiodarone (200mg) daily
- Pantoprazole (40mg) daily

Print and give pt.
Show Hx of medications
Drug/Herb Interactions

The eMERGE Network
Electronic Medical Records & Genomics
Pharmacogenomics Research Network
Adverse and Allergic Drug Reactions:
- Aldometone (ralat)
- Drug Genome Interactions: (01/03/13 13:04)
  - 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: SLCO1B1 - gene result: *5/*5
  - thiopurine sensitivity: INTERMEDIATE MYELOTOXICITY RISK, MINOR ALLELE HETEROZYGOUS - gene: TPMT - gene result: *1/*3c

Note: Most genetic variants with therapeutic considerations demonstrate reproducibility of greater than 93%. Please visit www.mydruggenome.org for additional information.

Medications:
- Simvastatin (zocor) 20 mg orally nightly
- Quinapril (acepril) 40 mg orally daily
- Zolpidem (ambexa) 10 mg orally daily
- Carvedilol (coreg) 6.5 mg orally twice daily with meals
- Furosemide (lasix) 20 mg 3 tablets orally daily
- Diclofenac (lanoxic) 0.125 mg 1/2 tablet orally daily
- Warfarin (coumadin) 2 mg, 2 tablets on sun by month and 1 1/2 tablet on other days
- Potassium (k-dur) 10 mEq 3 tablets orally daily
- Multivitamin (centrum algae) dose unknown daily
- Ampicloxone 200 mg tablet 0.5 tablet by mouth daily
- Prilosec 40 mg by mouth daily as needed
- Spirinolactone 25 mg 1/2 tablet by mouth daily

Structured Problems:
- Coronary artery disease []
- Aortic valve stenosis [severe]
- Congestive heart failure []
- Mitral valve regurgitation []
- Chronic atrial fibrillation []
- Hypertension []
- Hyperlipidemia []
- Gastroesophageal reflux disease []
- 9. Chronic Renal insufficiency
- Paroxysmal ventricular tachycardia
- PVTach cardiac arrest, 9/12/09
- ICD Shock for VVTach, 9/14/2010
- Hx Blood Transfusion:
- Anesthesia Difficulties:
- Dental Hygiene:
- Emergent:

Consults:
- ED DIC App
- Inpt. census
- Outpt. visits
- PatientsView
- Panels
- Roden-DMD
- Recent pts.
- StarVisit
- Scratch cens.
- Teams cen.
- Work lists

Inf. Resources:
- Look
- Logout
- Patient search

Consults
- AuthorizeAccess MHaVFulAccess Who documented? Remove.PCW.Contacts
- Search:
  - Title: 
  - Author: 
  - FullText
  - Customize
  - NoFilter
  - All
  - My
  - anat
  - pat
  - clin.com
  - disch sum
  - forms
  - image
  - intake
  - labs
  - notes
  - orders
  - radcal
  - rehab
  - resp
  - rc

User rodewalt (Roden, Dan M.) documents results: 16

PharmacoGenomics Research Network

The eMERGE Network
electronic Medical Records & Genomics
### Patient-specific guidelines

**Structured Problems:**

- Coronary artery disease [ ]
- Aortic valve stenosis (severe) [ ]
- Congestive heart failure [ ]
- Mitral valve regurgitation [ ]
- Chronic atrial fibrillation [ ]
- Hypertension [ ]
- Hyperlipidemia [ ]
- Gastroesophageal reflux disease [ ]
- 9. 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: Emergent [ ]

### Adverse and Allergic Drug Reactions:

- Aldactone (naxil)

### Drug Genome Interactions:

<table>
<thead>
<tr>
<th>Date</th>
<th>Title</th>
<th>Author</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/14/13</td>
<td>Consult Request for Willers, Elisabeth D.</td>
<td>Roden, Dan M.</td>
<td></td>
</tr>
<tr>
<td>01/11/13</td>
<td>Clin.Comm. (PFT's Results)</td>
<td>Strickland, Teresa</td>
<td></td>
</tr>
<tr>
<td>12/13/12</td>
<td>Orders (Labs)</td>
<td>Strickland, Teresa</td>
<td></td>
</tr>
</tbody>
</table>
10,489 PREDICT patients (9/2010-1/2013)

Clopidogrel (CYP2C19*2)  
↑risk of drug failure  
high risk: 2.7%  
any risk: 21.7%

Simvastatin (SLCO1B1*5)  
↑risk of muscle pain  
high risk: 1.9%  
any risk: 25.7%
Multiplex testing for pharmacogenetic variants

Risk Variants
- CYP2C19 *2-*8
- SLOC1B1 *5
- CYP2C9 / VKORC1
- TPMT *2-*3

Total n=10,489
PharmacoGenomics Research Network

Point-of-care Decision Support

Clopidogrel Poor Metabolizer Rules

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

This patient has been tested for CYP2C19 variants, and the presence of the *2/*2 genotype has identified this patient as a poor metabolizer of clopidogrel. Poor metabolizers treated with clopidogrel at normal doses exhibit higher rates of stent thrombosis/other cardiovascular events.

Treatment modification is recommended:

- Prescribe prasugrel (EFFIENT) 10mg daily and stop clopidogrel (PLAVIX) start date, 10 AM

Due to increased risk of bleeding, prasugrel should not be given to patients:

- that have a history of stroke or transient ischemic attack
- that are greater than 75 years of age
- whose body weight is less than 50 kg

Click here for more information.

If prasugrel (EFFIENT) not selected, please choose desired action:

- Increase maintenance dose of clopidogrel (PLAVIX) 150 mg daily, start date, 10AM
- Maintain requested daily dose of clopidogrel (PLAVIX) 75 mg daily, start date, 10AM

- Contraindicated
- Expected effects (e.g. nuisance bleeding)
- Patient preference
- Other

Click here for more information.

NOTE: The Vanderbilt P&T Committee has recommended that prasugrel (if not contraindicated) should replace clopidogrel for poor metabolizers; if this is not possible consider doubling the standard dose of clopidogrel (or, use standard dose clopidogrel). However, there is not a national consensus on drug/dose guidance in this population.
Antiplatelet Drug Selection by CYP2C19 Phenotype

Proportion Prescribed Drug

- Poor Metabolizer (N=32): 53% Clopidogrel, 47% Prasugrel
- Intermediate Metabolizer (N=305): 79% Clopidogrel, 21% Prasugrel
- Indeterminate (N=122): 93% Clopidogrel, 6% Prasugrel, 0.8% Ticagrelor
- Normal (N=1079): 94% Clopidogrel, 6% Prasugrel, 0.4% Ticagrelor

p<10^{-14}
Decision Support for Warfarin Initial Dose

The advisor appears in the black box and shows the Recommended initial WEEKLY & DAILY dose.

Links to clinical evidence and dosing table.
Warfarin advisor – Week 1

- 31 new inpatient starts of warfarin recorded in EMR
- 7/31 had received PREDICT testing
- 2/7 had genetic differences

Take home: Only 6/32 patients were started on the “traditional” dose of 5mg daily
**Warfarin CDS Surveillance Example**

**Recommended Daily Dose = 9 mg/d**

**Initial Dose Prescribed = 1 mg/d**

Gene Results = warfarin normal responder

Recommended Weekly Dose = 63.0

Amiodarone = 0

Inducer = 0

Age = 39

Height = 180

Weight = 78.5

[Graph showing INR and Daily Dose over time]

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PharmacoGenomics Research Network

The eMERGE Network
electronic Medical Records & Genomics
eMERGE-PGx – Overall Goal

To initiate a multi-site test of the concept that sequence information can be coupled to electronic medical records for use in healthcare

- Started in 2007 – 5 sites; now – 9 sites
- Each has ≥3000 GWAS EMR patients
- **Goal**: to perform GWAS for ~40 phenotypes with existing samples
- **Translate to clinical practice**
eMERGE-PGx: a PGRN-eMERGE alliance

**Pharmacogenomics Research Network (PGRN)**
- Clinical Pharmacogenomics Implementation Consortium (CPIC)
- Translational Pharmacogenomics Project (TPP)
- PGRN-Seq and other platforms

**eMERGE**
- developing and validating electronic phenotyping algorithms (including for drug responses)
- integration with EHR
- developing and deploying clinical decision support
The vast majority of sequence variation across exomes is rare...

...and most variants seen are missense

Tennessen et al., 2012
eMERGE-PGx Aims

Aim 1

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

Identify target patients

Resequence VIP genes; Identify actionable variants

The eMERGE Network
electronic Medical Records & Genomics
eMERGE-PGx Aims

Aim 1

Identify target patients

Resequence VIP genes; Identify actionable variants

Aim 2

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

Actionable variants

EMR deposit
- Result display
- Decision support

Outcomes
- Performance metrics
- Healthcare impact
eMERGE-PGx Aims

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

Develop list of actionable variants (eMERGE, CPIC, …)
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
• **PGRN-Seq is available for use by others**
Mean Read Depth per Individual
Mean Read Depth per Gene

- **VKORC1**
- **CYP2C19**
- **CYP2C9**
- **SLCO1B1**
PGRN-Seq: Status/issues

- Comparison to Illumina ADME: 88/95 HapMap samples concordant at ~150 sites
- 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
# PGx candidate drug-gene pairs

<table>
<thead>
<tr>
<th>Gene</th>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>clopidogrel</td>
<td>Best evidence in patients with coronary stents</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Warfarin</td>
<td>Algorithms to predict starting dose available. Vary by ancestry</td>
</tr>
<tr>
<td>VKORC1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP4F2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>Simvastatin</td>
<td>Especially at higher dosages or with interacting drugs</td>
</tr>
<tr>
<td>TPMT</td>
<td>Thiopurines (6-MP, azathioprine)</td>
<td></td>
</tr>
</tbody>
</table>
## 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>
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<tr>
<td>Northwestern</td>
<td>3</td>
<td>44</td>
<td>0</td>
<td>191</td>
<td>512</td>
<td>750 (62)</td>
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<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><strong>Total</strong></td>
<td><strong>21</strong></td>
<td><strong>172</strong></td>
<td><strong>1</strong></td>
<td><strong>1426</strong></td>
<td><strong>6269</strong></td>
<td><strong>7889 (53)</strong></td>
</tr>
</tbody>
</table>
Patient selected for genotyping via predictive algorithm - consented for study

PGRN-Seq
84 genes

Validation of Target Genotypes

Genotype DB

Select variants put into EMR
- Validated
- Decision support
- Local eMERGE site clinical buy-in (e.g., P&T committees)

Variants of Unknown Significance outside EMR
- New research for drug-genome interaction discovery
- eMERGE PGx Variant Repository
## Genotyping sites and validation

<table>
<thead>
<tr>
<th>Site</th>
<th>Sequencing*</th>
<th>Validating*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NU</td>
<td>CIDR</td>
<td>Mt. Sinai: ADME</td>
</tr>
<tr>
<td>Geisinger</td>
<td>Geisinger</td>
<td>Geisinger: Taqman</td>
</tr>
<tr>
<td>GHC/UW</td>
<td>UW (Nickerson)</td>
<td>CIDR Sequenom</td>
</tr>
<tr>
<td>Mayo</td>
<td>Mayo</td>
<td>Mayo: Sanger</td>
</tr>
<tr>
<td>Vanderbilt</td>
<td>CIDR</td>
<td>Vanderbilt: Illumina ADME</td>
</tr>
<tr>
<td>Marshfield</td>
<td>UW (Nickerson)</td>
<td>Marshfield: Sequenom</td>
</tr>
<tr>
<td>Mt. Sinai</td>
<td>Mt. Sinai</td>
<td>Mt. Sinai: ADME</td>
</tr>
<tr>
<td>CHOP</td>
<td>CHOP</td>
<td>CHOP: Illumina ADME/sanger</td>
</tr>
<tr>
<td>BCH/CCMH</td>
<td>UW (Nickerson)</td>
<td>BCH/CCMH: PCR (CYP2D6)</td>
</tr>
</tbody>
</table>

*All sites will have extra genotyping and Sequenom validation at CIDR*
# Initial target drugs

<table>
<thead>
<tr>
<th>Institution</th>
<th>Target Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NU</td>
<td>clopidogrel, warfarin, simvastatin</td>
</tr>
<tr>
<td>Geisinger</td>
<td>clopidogrel, warfarin, simvastatin</td>
</tr>
<tr>
<td>GHC/UW</td>
<td>carbamazepine (other pairs implemented at UW)</td>
</tr>
</tbody>
</table>
| Mayo        | clopidogrel, warfarin, simvastatin  
  Also: abacavir, interferon, thiopurines, carbamazepine |
| Vanderbilt  | clopidogrel, warfarin, simvastatin, thiopurines |
| Marshfield  | clopidogrel, warfarin, simvastatin |
| Mt. Sinai   | clopidogrel, warfarin, simvastatin |
| CHOP        | carbamazepine, thiopurines |
| BCH/CCMH    | codeine (using local PCR) |
## Subject selection

<table>
<thead>
<tr>
<th>Institution</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>NU</td>
<td>Predictive algorithm from internal medicine clinics</td>
</tr>
<tr>
<td>Geisinger</td>
<td>Predictive algorithm to MyCode® population and identified candidates.</td>
</tr>
<tr>
<td>GHC/UW</td>
<td>Predictive algorithm to identify 900 subjects. A subset of 450 will be selected for confirmatory testing and return of results.</td>
</tr>
<tr>
<td>Mayo</td>
<td>Predictive algorithm.</td>
</tr>
<tr>
<td>Vanderbilt</td>
<td>Predictive algorithm among general outpatient population</td>
</tr>
<tr>
<td>Marshfield</td>
<td>Predictive algorithm</td>
</tr>
<tr>
<td>Mt. Sinai</td>
<td>Predictive algorithm</td>
</tr>
<tr>
<td>CHOP</td>
<td>Cross-reference the CAG biobank with CHOP’s adverse events database.</td>
</tr>
<tr>
<td>BCH/Cinn</td>
<td>6-18 year olds evaluated for idiopathic scoliosis or pectus excavatum</td>
</tr>
</tbody>
</table>
# CLIA Validation of PGRN-Seq (CIDR)

<table>
<thead>
<tr>
<th>(Initial) Drug target</th>
<th>Primary Variant(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>clopidogrel</td>
<td>CYP2C19 *2</td>
</tr>
<tr>
<td></td>
<td>CYP2C19 *3</td>
</tr>
<tr>
<td></td>
<td>CYP2C19 *4</td>
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<tr>
<td></td>
<td>CYP2C19 *5</td>
</tr>
<tr>
<td></td>
<td>CYP2C19 *6</td>
</tr>
<tr>
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<td>CYP2C19 *7</td>
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<td>simvastatin</td>
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Integration with the EHR

- eMERGE EHR Integration working group
- EHRs: Epic, GE, Cerner, homegrown
- Store variants of known significance in structured ways
- Need to develop electronic decision support advisors
- Working with HL7 standards groups
Future eMERGE-PGx Variant Server

- Genetic variant database
- Phenotype Database (PGx record counter)
- Biological function database (PharmGkB)

Web interface to query

Login: some data public, some private

Query by gene
Query by variant
Query by phenotype

Link to look up functional and/or experimental results
Phenotype Database

• Very much in development
• Likely will be limited to broadly-available, non-curated EMR phenotype data
• Demographics (Age, Gender, Race/Ethnicity)
• Diagnosis and procedure codes (ICD9, CPT)
• Medication exposures (based on prescriptions)
• Potential for a few “detailed PGx phenotypes” related to specific drug exposures
Process Measures

- Very much in development
- Surveys of providers and patients
- Accrual measures
- Performance of PGRN-Seq compared to validation methods
- Genotype distributions
- Patient views of genetic data in Patient Portals
- Number of patients who get prescribed target medications over time
- Adherence to genome-guided recommendations
- Outcomes on rare variants with target medications
Prospective for collaborations

- Use of PGRN-Seq platform
- Sharing of data in central repository from eMERGE
- Placing data into repository
eMERGE-PGx leadership:
• Laura Torvik-Rasmussen
• Dan Roden
• Josh Denny

eMERGE Sites:
• Boston Children’s
• Children’s Hospital of Philadelphia
• Cincinnati Children’s
• Geisinger Health System
• Group Health/Univ of Washington
• Marshfield
• Mayo
• Mount Sinai
• Northwestern
• Vanderbilt

PREDICT leadership:
• Dan Roden
• Jill Pulley
• Erica Bowton
• Josh Peterson
• Josh Denny

PGRN-Seq:
• Debbie Nickerson
• Steve Scherer

EHR Integration WG leaders:
• Erwin Bottinger
• Justin Starren