PGx Implementation Research Programs at Vanderbilt

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5/2/17
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
EHR feeds both discovery and implementation

Discovery

De-identified DNA repository
>235k samples

Implementation

PREDICT, IGNITE, (eMERGE)
- CLIA genomics lab
- Integrated decision support for genomics
- Genomic databases
- Track outcomes
Discovery: Resources for EMR-based research at Vanderbilt

The Synthetic Derivative
A de-identified and continuously-updated image of the EMR: ~2.5 million subjects

BioVU
Subjects with DNA: ~235k
EHRs for drug response:
Clopidogrel adverse events associated with *CYP2C19* status

From clinical trials

- Carriers: 12.1%
- Non-carriers: 8.0%

\[ N=1459, \ P=0.01 \]

From the EHR

\[ N=807, \ P=0.005 \]

Mega et al., 2009

Delaney et al. *Clin Pharm Ther.* 2012
How do we routinize PGx implementation?

PREDICT: Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment

"Here's my sequence..."

New Yorker, 2000

...the right drug, the first time.
A Case for Prospective Genotyping:
identifying a **high risk** group

52,942 Vanderbilt “Medical Home” patients followed for up to 5 years....

**How many patients received drug(s) that have a recognized pharmacogenetic story?**

<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>
<tr>
<td>4</td>
<td>5244</td>
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<tr>
<td>5</td>
<td>3883</td>
</tr>
<tr>
<td>6</td>
<td>2870</td>
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<td>7</td>
<td>2067</td>
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<tr>
<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>

65% received ≥1 med within 5 years

Estimated number of severe adverse events mitigated: 383 (~12-18 events for the average PCP over 5 years)

Schildcrout et al, CPT 2012
Provider Opinions

Surveyed 121 VU providers encountering PGx prescribing; 80 responded (66% response rate)

- A patient’s genetic profile may influence his/her response to drug therapy
- Pharmacogenomic testing prior to prescribing clopidogrel assists with anti-platelet therapy decisions.
- Pharmacogenomic-guided antiplatelet therapy will reduce the likelihood in-stent thrombosis.
- Pharmacogenomic testing is useful for directing the dose of warfarin therapy
- Pharmacogenomic testing prior to warfarin prescription will reduce the likelihood of an adverse drug event
Factors influencing ordering of PGx tests

- Strength of evidence that genetic test results could affect my patients' drug selection dose
- Absence of out-of-pocket cost to the patient
- Recommendations by thought leaders or respected colleagues
- Recommendations by guidelines or the Food and Drug Administration
- My interest in knowing my patients' genetic susceptibility for drug response
- Inclusion of pharmacogenomic test with an order set
- Knowing that pharmacogenomic testing is an institutional priority
- My patient's interest in knowing their genetic susceptibility for drug response
- Being prompted by an alert within the Electronic Medical Record
Selection of PREDICT Drug-Gene Interactions

- Evidence Review
- Guidance: Professional Societies, FDA
- Replication in Vanderbilt population (BioVU)
- Review and Approval by P&T Committees
- Implementation including automated decision support
Genetic results visible passively in EHR

Drug Genome Interactions in the Patient Summary

Adverse and Allergic Drug Reactions: (02/21/13 12:25, Teresa)

Aldactone (rash)

Drug Genome Interactions: (01/05/12 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: SLCO1B1 - gene result: *5/*5
thiopurine 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 for additional information.

Medications: prepare to print print and give pt Show Hx of medications Drug/Herb Interactions (02/21/13 12:25, Teresa)

Simvastatin (zocor) 20 mg orally nightly
Quinapril (acupril) 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
Clinical Decision Support within E-Prescribing

Drug-Genome Advisor
Intermediate Metabolizer - clopidogrel (Plavix) - Rare Risk Allele
Substitution recommended due to increased cardiovascular risks

If not otherwise contraindicated:

☐ Prescribe prasugrel (Effient) 10 mg daily

Prasugrel should not be given to patients:
• history of stroke or transient ischemic attack
• >= 75 years of age [Current patient age: 51]
• with body weight < 60 kg [Current patient weight: 59.0 kg as of 10/12/2012]

☐ Prescribe ticagrelor (Brilinta) 90 mg twice daily

Ticagrelor should not be given to patients:
• history of severe hepatic impairment
• intracranial bleed

☑ Continue with clopidogrel (Plavix) prescription

Primary override reason:
☐ Contraindicated for prasugrel or ticagrelor
☐ Potential side effects
☐ Provider/Patient opts for clopidogrel
☐ Cost

Evidence Link

This patient has been tested for CYP2C19 variants which has identified the presence of one copy of a rare risk allele which is associated with intermediate metabolism of clopidogrel. Intermediate metabolizers treated with clopidogrel at normal doses are associated with higher rates of stent thrombosis and other cardiovascular events. The Vanderbilt P&T Committee recommends that prasugrel or ticagrelor replace clopidogrel for poor metabolizers unless contraindicated. If not feasible, maintain standard dose of clopidogrel. The guidelines above were developed based on the outcome studies of patients who received a drug-eluting stent into a coronary artery. However, there is not a national consensus on drug/dose guidance particularly associated with the population possessing extremely rare genetic variants.
At least one high risk variant

At least one actionable variant

No actionable variants

91% Frequency of actionable genotypes in the first 10,000 PREDICT patients

Van Driest, CPT 2014
Multiplexed Genetics Testing can save money too

Van Driest et al, Clin Pharmacol Therap. 2014
Do providers follow recommendations?

Genotype tailored therapy

<table>
<thead>
<tr>
<th>Rate</th>
<th>Adjusted HR</th>
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<tbody>
<tr>
<td>58%</td>
<td>8.1 (5.4, 12.1)</td>
</tr>
<tr>
<td>33%</td>
<td>5.0 (4.0, 6.3)</td>
</tr>
<tr>
<td>8%</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Log rank p < 0.001
IGNITE CPIC Prescribing Study: Antiplatelet drugs

Clopidogrel remains the most commonly prescribed antiplatelet drug
IGNITE CPIC Prescribing Study: Anticoagulants

Warfarin still most frequent anticoagulant except at VA
Increasing Adoption at Sanford Health (part of our IGNITE site)

IGNITE clopidogrel data presented at AHA
Preliminary results - Evaluating cost effectiveness

<table>
<thead>
<tr>
<th>PGx Scenario</th>
<th>Incremental cost effectiveness ratio of genotyping</th>
</tr>
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<tbody>
<tr>
<td>Clopidogrel – CYP2C19</td>
<td>$36,618</td>
</tr>
<tr>
<td>Simvastatin – SLC01B1</td>
<td>$1,405,163</td>
</tr>
<tr>
<td>Warfarin – CYP2C9/VKORC1</td>
<td>$371,649</td>
</tr>
</tbody>
</table>

beta site: https://rightsim.org/RIGHT/
A few of the lessons learned

• Implementation is about the lab, process, EHR, and people
  • PGx is a “bleeding edge” of lab tests
  • MU-mediated EHR upheaval
  • Each EHR implementation has been different

• Local provider buy-in driven by 1) belief in clinical efficacy, 2) ease of use (e.g., CDS), 3) familiarity

• Advice changes frequently and opportunities to (re)use data accrue over time
  • Need for surveillance
What personalizing medicine really means

57yo with DM2, FHx heart disease, ↑chol admitted for chest pain, receives stent

In-stent thrombosis, restent
Recath, stent
"Plavix x 1 year minimum. ASA life long."

In-stent thrombosis, restent
Cath, more stents

9th admission, 5th intervention, 9th stent
CYP2C19*2/*2 clopidogrel poor metabolizer

Switched to prasugrel

January

April
clopidogrel started

December

VANDERBILT UNIVERSITY MEDICAL CENTER
A sampling of the team