Implementing personalized medicine strategies in 2014: the academic perspective

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Vanderbilt University School of Medicine
Personalized medicine – not a new idea

Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease.

Sir William Osler
Two faces of pharmacogenetics

Serious ADRs

Variability in efficacy

Pharmacogenomics Research Network
Mephenytoin hydroxylation deficiency in Caucasians: Frequency of a new oxidative drug metabolism polymorphism

Departments of Medicine and Pharmacology, Vanderbilt University

December 1984

Cumulative urinary recovery of 4-hydroxy-mephenytoin (μmol)

Time (hours)

S-Mephenytoin 4-hydroxylase = CYP2C19
The vision

"Here's my sequence..."

New Yorker, 2000

Collins: Pharmacogenomics will undoubtedly become a very compelling part of medical practice. The limiting factor right now is that oftentimes, if you are ready to write a prescription, you do not want to wait a week to find out the genotype before you decide whether you've got the right dose and the right drug. But if everybody's DNA sequence is already in their medical record and it is simply a click of the mouse to found out all the information you need, then there is going to be a much lower barrier to beginning to incorporate that information into drug prescribing. If you have the evidence, it will be hard, I think, to say that this is not a good thing. And once you've got the sequence, it's not going to be terribly expensive. And it should improve outcomes and reduce adverse events.

Francis Collins, NEJM 9/16/2009
Discovery

Studying cohorts
• in very large research datasets
• in targeted settings

Clinical implementation

Using a highly interactive electronic medical record
• to provide real-time clinical advice
• to track outcomes
BioVU, the Vanderbilt DNA bank

A **discovery resource** for genomics and pharmacogenomics, linking DNA samples to de-identified electronic medical records

"Here's my sequence…"

*New Yorker, 2000*
Potential projects in a very large set like this

(1) Searching for genomic variants associated with specific phenotypes:
   • Physiologic traits
   • Disease; disease progression
   • Drug responses

(2) Searching for phenomic variants associated with specific DNA polymorphisms (PheWAS)

(3) Drug target discovery
What is the Phenotype KnowledgeBase?

The reuse of data from electronic medical records (EMRs) and other clinical data systems holds tremendous promise for improving the efficiency and effectiveness of health research. Clinical data in the EMR is a potential source of rich longitudinal data for research, and the recent government efforts to promote the use of EMRs in the clinical setting may further promote the use of such systems in the US healthcare system. As the use of EMRs expands, the demand for usable data from these systems for research has also expanded.

One such effort by the Electronic Medical Records and Genomics Network (eMERGE) has investigated whether data captured through routine clinical care using EMRs can identify disease phenotypes with sufficient positive and negative predictive values for use in genome-wide association studies (GWAS). Most EMRs captured key information (diagnoses, medications, laboratory tests) used to define phenotypes in a structured format; in addition, natural language processing has also been shown to improve case identification rates.*

PheKB is an outgrowth of that validation effort and provides a collaborative environment of building and testing validated phenotype algorithms.

*Disclaimer: This information is not intended to be a replacement for professional medical advice.
The phenome-wide association study

GWAS:
- Target phenotype
- chromosomal location
- association
- P value

PheWAS (ΦWAS):
- Target genotype
- diagnosis code
- association
- P value

PheWAS requirement: A large cohort of patients with genotype data and many diagnoses
Pleiotropy: PheWAS associations with an IRF4 SNP previously associated with hair and eye color

N=13,385

Denny et al., 2013
Pleiotropy: PheWAS associations with an IRF4 SNP previously associated with hair and eye color

- All SNPs in the GWAS catalog have now been analyzed by PheWAS
- PheWAS provides a replication tool for conventional GWAS and identifies potential new genetic associations
- All data are publically available at emrphewas.org

Denny et al., 2013
15th century disease definitions

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<td>Abovity and Stilborne</td>
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<tr>
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<td>Appoplexy and Suddenly</td>
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<td>Bedrid</td>
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<td>Blasted</td>
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<tr>
<td>Bleeding</td>
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<tr>
<td>Bloody Flux, Scouring &amp; Flux</td>
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<td>Burnt and Scalded</td>
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<tr>
<td>Calement</td>
<td>3</td>
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<tr>
<td>Cancer, Gangrene and Fistula</td>
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<td>Cancer, and Thurst</td>
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<td>Childbed</td>
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<td>Executed</td>
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<td>Flog and Small Pox</td>
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<td>Found dead in streets, fields, &amp;c.</td>
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<td>French Fever</td>
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<td>Headmouldshot &amp; Mouldfallen</td>
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<td>Jaundies</td>
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<tr>
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<td>Impostume</td>
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<td>Livergrown</td>
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<td>Rickets</td>
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<tr>
<td>Rupture</td>
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<tr>
<td>Scoury</td>
<td>105</td>
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<tr>
<td>Shingles and Swine pox</td>
<td>2</td>
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<tr>
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<tr>
<td>Spleen</td>
<td>14</td>
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<tr>
<td>Spotted Fever and Purples</td>
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<tr>
<td>Vomiting</td>
<td>51</td>
</tr>
<tr>
<td>Venen</td>
<td>5</td>
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BRAF Inhibition in Refractory Hairy-Cell Leukemia

TO THE EDITOR: Hairy-cell leukemia (HCL) is a mature B-cell lymphoid cancer that is commonly treated with purine analogues.¹ Virtually all patients with HCL carry the BRAF V600E mutation,
21\textsuperscript{st} century phenomics?

Hairy cell leukemia

Clinical descriptors
21st century phenomics?

Clinical descriptors
- B-cell malignancy
- BRAF V600E
- Expected response to
  - cladribine
  - vemurafenib
  - ...

Medication response

Lab data:
- Histology
- Biomarkers
- Genomics
- Histology
- ...

Hairy cell leukemia
EMR-linked biobanks in eMERGE

<table>
<thead>
<tr>
<th>Site</th>
<th>Participants</th>
<th>(GWAS)-Genotyped Samples</th>
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<tbody>
<tr>
<td>Mt. Sinai</td>
<td>25,000</td>
<td>6,545</td>
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<tr>
<td>CHOP</td>
<td>60,000</td>
<td>6,623</td>
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<tr>
<td>Cincinnati/Boston</td>
<td>11,844</td>
<td>6,596</td>
</tr>
<tr>
<td>TOTAL</td>
<td>360,703</td>
<td>56,955</td>
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A paradox, and an opportunity...
Large numbers of patients, of diverse ancestries, are required to develop evidence to “personalize” medicine.
Studying cohorts
• in very large research datasets
• in targeted settings

Using a highly interactive electronic medical record
• to provide real-time clinical advice
• to track outcomes

Discovery

Clinical implementation
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.
One “high risk” group

A case for preemptive genotyping; Schildcrout et al., 2012

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”?

→ Develop and deploy methods to tag “high risk” patients in the EMR environment
Clopidogrel label revision March 2010 identifies another **high risk** group

**WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS**

See full prescribing information for complete boxed warning.

- Effectiveness of clopidogrel for platelet inhibition and thrombosis prevention, principally **CYP2C19** (5.1)
- Poor metabolizers, defined as patients with low plasma concentrations of the active metabolite of clopidogrel, are at increased risk of cardiovascular events such as nonfatal myocardial infarction (MI), stroke, and death when treated with clopidogrel after acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 activity (5.3)
- Tests are available for determination of the patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)
**General Information:** (12/03/12 09:03, Teresa)

PCP: 
Card: 
Arhythmia/Device: Dr. Dan Roden, VUMC

**Structured Problems:** (12/03/12 09:05, Teresa)

- 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

**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
- 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, Mena, Lassley C for Pugh, Meredith E.)

- Simvastatin (zocor) 20 mg orally nightly
- Quinapril (accupril) 40 mg orally daily
- Zolpidem (ambien) 10 mg 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) 10 meq 3 tablets orally daily
CYP2C19 genotypes in 13,421 PREDICT patients (9/2010-6/2013)

- 2.7% homozygous
- 19.4% heterozygous
- 11.7% non-actionable variant
- 66.3% no common variant
Point of care decision support

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

Order  Cancel

NOTE: The Vanderbilt P&T Committee recommends that prasugrel or ticagrelor replace clopidogrel for poor metabolizers unless contradicted, 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.
Multiplexed testing for pharmacogenetic variants
(after 5 drug-gene pairs...)

Total n=13,451
(9/10-6/13)

- 0 variants (11.7%)
- 1 variant (29.5%)
- 2 variants (31.7%)
- 3 variants (18.4%)
- 4 variants (6.8%)
- ≥5 variants (1.9%)
eMERGE-PGRN Partnership

PGx capabilities:
- Array-based assay for pharmacogenes
- Drug-gene guidelines

EMR-informatics capabilities
- Privacy
- Electronic phenotyping
- Large populations

The eMERGE Network
Electronic Medical Records & Genomics
eMERGE-PGx project

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, …)

Identify actionable variants

Outcomes
What are the barriers?

- What is personalized medicine? who decides?
- Evidence base may be controversial
- Outcomes in targeted subsets may be especially difficult to demonstrate
- Participation and buy-in required from multiple stakeholders. Ethical balance.
- Informatics needs are large, and extend beyond simply managing data
- Who pays? Will total costs fall?
- Educational imperatives
What are the opportunities?

• Better care: less time on ineffective therapies, potential to increase compliance
• Develop and refine new technologies (e.g. informatics/the electronic record) with multiple potential collateral benefits
• Identifying new biomarkers of disease leads to unprecedented opportunities in mechanism-based science
The Teams

The eMERGE Network
electronic Medical Records & Genomics
A consortium of repositories linked to electronic medical records data for conducting genomic studies

Pharmacogenomics Research Network