Using Electronic Medical Records to advance genomic medicine

Josh Denny, MD, MS
Vanderbilt University, Nashville, Tennessee, USA

20th International Symposium on Microsomes and Drug Oxidations
5/19/2014
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..."

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How will this vision actually start to be tested and become reality?

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

“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
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**

Vanderbilt BioVU
De-identified DNA repository
>160k samples

**Implementation**

PREDICT
- CLIA genomics lab
- Integrated decision support for genomics
- Predictive algorithms on who to test
- Genomic databases
- Track outcomes
Vanderbilt BioVU: an Opt-Out DNA Biobank

Extracting DNA from left over blood samples
Vanderbilt BioVU: an Opt-Out DNA Biobank

Extracting DNA from left over blood samples

I also understand that if I do not want DNA research to be done using my leftover blood, I need to check the box shown below. If you have questions, please call 1-866-436-4710.

☐ Do not use my leftover blood for the DNA Databank

(CENT FOR TREATMENT AND AGREEMENT TO PAY (ADULT))

(CENT FOR TREATMENT AND AGREEMENT TO PAY (ADULT))

I hereby authorize the performance of all nursing and technical procedures and tests as directed by my physician(s) and consent to the administration of blood products.
Vanderbilt BioVU: an Opt-Out

DNA Research

Leftover blood from tests, treatment, or surgery may also be used for DNA research through the Vanderbilt BioVU Program. If I do not want my leftover blood to go to the Vanderbilt BioVU Program for DNA research, I must check the box below. If I have questions or want further information on BioVU, I may call 866-436-4710.

☐ I do NOT want blood left over from my tests, treatment, or surgery to be used for the Vanderbilt BioVU Program for DNA research.

Please click "Next" and write your name on the next screen.

Next

Copies of the forms you sign are available upon request.
One way hash

John Doe

~2 million records

The Synthetic Derivative: updated regularly

A7CCF9DE65732.....
One way hash

~2 million records

The Synthetic Derivative: updated regularly

Scrubbed

A7CCF9D6E5732...
One way hash

John Doe

eligible?

John Doe

~2 million records

The Synthetic Derivative:
updated regularly

scrubbed

A7CCF99DE65732....
The Synthetic Derivative: updated regularly

~2 million records

BioVU
~180,000 DNAs

Extract DNA

A7CCF99DE65732...

Scrubbed

One way hash

A7CCF99DE5732...

John Doe

eligible?

John Doe

~2 million records
Electronic Medical Record

- Labs, Radiology, Test Results
- Clinical Notes
- Provider orders and e-prescribing
- External Registries

De-ID

Natural Language Processing

- Notes and text results
- Structured results
- Concepts
- Meds
- Codes
- Tumor Registry
- STS
BioVU as a resource for discovery

<table>
<thead>
<tr>
<th>disease</th>
<th>marker</th>
<th>gene / region</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>rs2200733</td>
<td>Chr. 4q25</td>
<td></td>
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<tr>
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<td>Chr. 4q25</td>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>rs17234657</td>
<td>Chr. 5</td>
<td></td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>rs1000113</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>rs17221417</td>
<td>NOD2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs2542151</td>
<td>PTPN22</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>rs3135388</td>
<td>DRB1*1501</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs2104286</td>
<td>IL2RA</td>
<td></td>
</tr>
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<td></td>
<td>rs6897932</td>
<td>IL7RA</td>
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</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>rs6457617</td>
<td>Chr. 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs6679677</td>
<td>RSBN1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs2476601</td>
<td>PTPN22</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>rs4506565</td>
<td>TCF7L2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs12255372</td>
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<td>rs4402960</td>
<td>IGF2BP2</td>
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</table>

Ritchie et al., AJHG 2010
BioVU as a resource for discovery

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Ritchie et al., AJHG 2010
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Ritchie et al., AJHG 2010
What we learned - Finding phenotypes in the EMR

Billing codes
ICD9 & CPT
What we learned - Finding phenotypes in the EMR

Billing codes
ICD9 & CPT

Clinical Notes
(NLP - natural language processing)
What we learned - Finding phenotypes in the EMR

Billing codes
ICD9 & CPT

Clinical Notes
(NLP - natural language processing)

Medications
ePrescribing & NLP
What we learned - Finding phenotypes in the EMR

- Billing codes (ICD9 & CPT)
- Medications (ePrescribing & NLP)
- Clinical Notes (NLP - natural language processing)
- Labs & test results (NLP)
What we learned - Finding phenotypes in the EMR

- Billing codes (ICD9 & CPT)
- Clinical Notes (NLP - natural language processing)
- Medications (ePrescribing & NLP)
- Labs & test results (NLP)

True cases
What we learned - Finding phenotypes in the EMR

Algorithm Development and Implementation

- Identify phenotype of interest
- Case & control algorithm development and refinement
- Manual review; assess precision
- Deploy in BioVU
- Genetic association tests

Clinical Notes
(NLP - natural language processing)

Billing codes
ICD9 & CPT

Medications
ePrescribing & NLP

Labs & test results
NLP

True cases

≥95%
<95%
Coordinating Center: pediatric sites

eMERGE goals
• To perform GWAS using EMR-derived phenotypes
• To initiate implementation of actionable variants into the EMR

[Map of the eMERGE Network with logos of participating institutions and a map of the United States with stars indicating pediatric sites.]
Hypothyroidism: Can we do a “no genotyping” GWAS?

Domain experts define phenotype (VU)

Create initial EMR-based algorithm (VU)

Evaluate & refine

Case PPV=92.4%
Control PPV=98.5%

Denny et al., AJHG 2011
Hypothyroidism: “No-Genotyping” GWAS

Denny et al., AJHG 2011
eMERGE GWAS completed

<table>
<thead>
<tr>
<th>Site</th>
<th>Primary phenotype</th>
<th>Secondary Phenotypes</th>
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<tbody>
<tr>
<td>Group Health</td>
<td>Dementia</td>
<td>white blood cell counts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>monocyte count</td>
</tr>
<tr>
<td></td>
<td></td>
<td>herpes zoster NEW</td>
</tr>
<tr>
<td>Marshfield</td>
<td>Cataracts</td>
<td>diabetic retinopathy</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>Peripheral Arterial Disease</td>
<td>red blood cell counts NEW</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ESR levels NEW</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Platelet levels</td>
</tr>
<tr>
<td>Northwestern</td>
<td>Type 2 Diabetes</td>
<td>HDL/LDL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>height</td>
</tr>
<tr>
<td>Vanderbilt</td>
<td>PR Duration</td>
<td>PheWAS NEW</td>
</tr>
<tr>
<td></td>
<td>QRS Duration</td>
<td></td>
</tr>
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</table>

Network Phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune Hypothyroidism</td>
<td>NEW</td>
</tr>
<tr>
<td>Resistant hypertension</td>
<td></td>
</tr>
</tbody>
</table>

**bold** = GWAS completed with significant results

**NEW** = first description or new findings

... another ~30 in progress as part of eMERGE II...
Extreme Phenotypes: LDL values in BioVU
Extreme Phenotypes: LDL values in BioVU

Analysis of ~32,000 BioVU subjects with existing exome chip data for LDL

<table>
<thead>
<tr>
<th>SNP</th>
<th>Phenotype</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCSK9 R46L</td>
<td>mean LDL</td>
<td>1.8x10^{-18}</td>
</tr>
<tr>
<td></td>
<td>minimum LDL</td>
<td>6.1x10^{-13}</td>
</tr>
<tr>
<td></td>
<td>LDL &lt; 50</td>
<td>1.9 x 10^{-6}</td>
</tr>
</tbody>
</table>
### Phenotype Cases Controls % Reuse

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Cases</th>
<th>Controls</th>
<th>% Reuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel in CV disease</td>
<td>225</td>
<td>468</td>
<td>27%</td>
</tr>
<tr>
<td>Warfarin stable dose</td>
<td>1,167</td>
<td>N/A</td>
<td>47%</td>
</tr>
<tr>
<td>Early Repolarization</td>
<td>544</td>
<td>2,609</td>
<td>89%</td>
</tr>
<tr>
<td>Vancomycin stable dose</td>
<td>1,067</td>
<td>N/A</td>
<td>42%</td>
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<tr>
<td>C. difficile colitis</td>
<td>941</td>
<td>1,710</td>
<td>28%</td>
</tr>
<tr>
<td>Anthracycline cardiomyopathy</td>
<td>528</td>
<td>N/A</td>
<td>39%</td>
</tr>
<tr>
<td>Guillain-Barre Syndrome</td>
<td>97</td>
<td>6,536</td>
<td>99%</td>
</tr>
<tr>
<td>Heart Transplant</td>
<td>181</td>
<td>N/A</td>
<td>42%</td>
</tr>
<tr>
<td>Kidney transplant</td>
<td>1,078</td>
<td>N/A</td>
<td>32%</td>
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<tr>
<td>Clopidogrel in strokes/TIAs</td>
<td>6</td>
<td>123</td>
<td>22%</td>
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<tr>
<td>Statin-related myopathy</td>
<td>11</td>
<td>4,342</td>
<td>100%</td>
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<tr>
<td>Heparin-induced thrombocytopenia</td>
<td>73</td>
<td>2,300</td>
<td>99%</td>
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<tr>
<td>CV events with COX2 therapy</td>
<td>85</td>
<td>395</td>
<td>34%</td>
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<tr>
<td>Serious bleeding during warfarin</td>
<td>259</td>
<td>276</td>
<td>43%</td>
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<tr>
<td>Amiodarone toxicity (lung, thyroid)</td>
<td>97</td>
<td>343</td>
<td>34%</td>
</tr>
<tr>
<td>Chronic inflammatory polyneuropathy</td>
<td>12</td>
<td>14,000*</td>
<td>100%</td>
</tr>
<tr>
<td>Rheumatic Heart Disease</td>
<td>108</td>
<td>3,464</td>
<td>98%</td>
</tr>
<tr>
<td>ACEi cough</td>
<td>1,174</td>
<td>978</td>
<td>52%</td>
</tr>
<tr>
<td>Fluoroquinolones and tenopathy</td>
<td>87</td>
<td>537</td>
<td>90%</td>
</tr>
<tr>
<td>Warfarin stable dose in children</td>
<td>92</td>
<td>N/A</td>
<td>28%</td>
</tr>
<tr>
<td>Metformin efficacy</td>
<td>80</td>
<td>N/A</td>
<td>35%</td>
</tr>
<tr>
<td>Metformin and cancer</td>
<td>619</td>
<td>421</td>
<td>83%</td>
</tr>
<tr>
<td>Bisphosphonates and Atypical Fracture/Jaw Osteonecrosis</td>
<td>16</td>
<td>1,454</td>
<td>99%</td>
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<tr>
<td>Wolff-Parkinson-White</td>
<td>197</td>
<td>5,551</td>
<td>97%</td>
</tr>
<tr>
<td>Steroid-induced Osteonecrosis</td>
<td>83</td>
<td>352</td>
<td>57%</td>
</tr>
<tr>
<td>Shellfish Anaphylaxis</td>
<td>157</td>
<td>14,000*</td>
<td>99%</td>
</tr>
<tr>
<td>Aspirin Anaphylaxis</td>
<td>101</td>
<td>4,334</td>
<td>98%</td>
</tr>
<tr>
<td>Bell's Palsy#</td>
<td>577</td>
<td>14,000*</td>
<td>97%</td>
</tr>
</tbody>
</table>

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Large scale GWAS for drug response discovery: the VESPA project

Vanderbilt Electronic Systems for Pharmacogenomic Assessment

clopidogrel \(\xrightarrow{\text{CYP2C19}}\) 2-oxoclopidogrel

clopidogrel failure = MI, stroke, revascularization, death following MI or PCI

**Semi-automated Methods**: Algorithms + Manual Review

n=225 cases / 468 controls

Delaney et al. *Clin Pharm Ther.* 2012
Predicting Warfarin Dose
Trained from the stable doses in the EMR

<table>
<thead>
<tr>
<th>SNP (Gene)</th>
<th>Beta</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1057910 (CYP2C9*3)</td>
<td>0.83</td>
<td>2.70x10^{-26}</td>
</tr>
<tr>
<td>rs9934438 (VKORC1)</td>
<td>0.87</td>
<td>4.48x10^{-61}</td>
</tr>
</tbody>
</table>

Ramirez et al. *Pharmacogenomics*. 2012
Two in-progress GWAS of Drug-ADEs from the EHR

ACEI-cough (NLP of allergy sections, automated)

Heparin-induced thrombocytopenia (automated+manual review)
The genome-wide association study

Target phenotype ➔ association n P value ➔ chromosomal location
The genome-wide association study

Target phenotype

Target genotype

chromosomal location

diagnosis code
The genome-wide association study

Target phenotype → association → chromosomal location

Target genotype → association → diagnosis code

PheWAS requirement: A large cohort of patients with genotype data and many diagnoses
PheWAS of “all” NHGRI GWAS Catalog SNPs
PheWAS of “all” NHGRI GWAS Catalog SNPs

3,144 SNPs with prior GWAS-discovered associations

NHGRI GWA Catalog
www.genome.gov/GWASudies

Denny et al, Nat Biotech 2013
PheWAS of “all” NHGRI GWAS Catalog SNPs

3,144 SNPs with prior GWAS-discovered associations

674 SNPs with 86 phenotypes
751 SNP-phenotype associations

Test for replication of 751 associations using PheWAS

Replication Arm

Denny et al, Nat Biotech 2013
PheWAS of “all” NHGRI GWAS Catalog SNPs

3,144 SNPs with prior GWAS-discovered associations

674 SNPs with 86 phenotypes
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Test for replication of 751 associations using PheWAS

Replication Arm

3,144 SNPs

PheWAS for each SNP to discovery pleiotropy

Replication of novel associations

Discovery Arm

Denny et al, Nat Biotech 2013
Replications of NHGRI GWAS associations via PheWAS

P-value for replication:
- All - 210/751: $2 \times 10^{-98}$
- Powered - 51/77: $3 \times 10^{-47}$

Denny et al, Nat Biotech 2013
PheWAS of all GWAS “hits”
Each dot=one phenotype

- GWA catalog association only
- GWA catalog association replicated by PheWAS
- New association found by PheWAS

Scale: n=21

Chromosome
PheWAS of all GWAS “hits”

Each dot = one phenotype

- GWA catalog association only
- GWA catalog association replicated by PheWAS
- New association found by PheWAS

PheWAS associations for TERT
Known: glioma
PheWAS of all GWAS “hits”
Each dot = one phenotype

- GWA catalog association only
- GWA catalog association replicated by PheWAS
- New association found by PheWAS

PheWAS associations for **IRF4**
Known: hair, skin, eye color

- basel-cell carcinoma
- carcinoma in situ of skin
- skin neoplasm of uncertain behavior
- benign neoplasm of eye
- benign neoplasm of skin
- mental disorders due to brain damage
- solar dermatitis
- seborrheic keratosis
- osteopenia

**Chromosome**
- **6p25.3**
- **9p21.3**
Using PheWAS to refine understanding of GWAS: normal cardiac conduction

SCN5A/SCN10A

n=5,272

Ritchie et al., Circulation 2013
“Phenome-wide association study” of rs6795970 (SCN10A)

N=13617 subjects with EHR data

Ritchie et al., Circulation 2013
What happens in the “heart healthy” population?

Examined 5272 “heart healthy” people

Followed for development of atrial fibrillation based on genotype

Ritchie et al., Circulation 2013
What happens in the “heart healthy” population?

Examined 5272 “heart healthy” people

Followed for development of atrial fibrillation based on genotype

Atrial fibrillation-free survival

HR=1.49 per G allele
p=0.001

Ritchie et al., Circulation 2013
The challenge of implementation

"Here's my sequence..."

New Yorker, 2000
PREDICT: Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment

- Multiplexed genotyping of 184 variants in 34 pharmacogenes
- Prospective + indication based testing
- Coupled with EHR-based Decision Support
- 4 Drug Genome Interactions tested:
  - Clopidogrel/CYP2C19
  - Warfarin/VKORC1+CYP2C9
  - Tacrolimus/CYP3A5
  - Thiopurines/TPMT

"Here's my sequence…"

New Yorker, 2000
A Case for Prospective Genotyping: identifying another 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?
A Case for Prospective Genotyping: identifying another 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?

65% received ≥1 med within 5 years

Schildcrout et al, CPT 2012
A Case for Prospective Genotyping: identifying another 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?

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

Schildcrout et al, CPT 2012
Patient comes in, selected for genotyping (cardiac cath, predictive algorithm, etc)

184 variants

Genotype DB

Select variants put into EMR
- Validated
- Computerized decision support
- Pharmacy and therapeutics committee

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
### Drug-Genome Advisor

**Intermediate Metabolizer - clopidogrel (Plavix) - Rare Risk Allele**

Substitution recommended due to increased cardiovascular risks

<table>
<thead>
<tr>
<th>If not otherwise contraindicated:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Prescribe prasugrel (Effient) 10 mg daily</td>
</tr>
<tr>
<td><strong>Prasugrel should not be given to patients:</strong></td>
</tr>
<tr>
<td>- history of stroke or transient ischemic attack</td>
</tr>
<tr>
<td>- &gt;= 75 years of age [Current patient age: 51]</td>
</tr>
<tr>
<td>- with body weight &lt; 60 kg [Current patient weight: 59.0 kg as of 10/12/2012]</td>
</tr>
<tr>
<td>- Prescribe ticagrelor (Brilinta) 90 mg twice daily</td>
</tr>
<tr>
<td><strong>Ticagrelor should not be given to patients:</strong></td>
</tr>
<tr>
<td>- history of severe hepatic impairment</td>
</tr>
<tr>
<td>- intracranial bleed</td>
</tr>
<tr>
<td>- Continue with clopidogrel (Plavix) prescription</td>
</tr>
</tbody>
</table>

**Primary override reason:**

- Contraindicated for prasugrel or ticagrelor
- Potential side effects
- Provider/Patient opts for clopidogrel
- Cost

---

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.
Testing for clopidogrel efficacy

clopidogrel $\xrightarrow{CYP2C19}$ 2-oxoclopidogrel

2.7% homozygous
18.9% heterozygous
78.4% no common variant

3% (inactive)
19%
78% (active)

↑risk of MI
Testing for clopidogrel efficacy

Clopidogrel \( \xrightarrow{\text{CYP2C19}} \) 2-oxoclopidogrel

- 78% no common variant
- 18.9% heterozygous
- 2.7% homozygous

\(|\uparrow\text{risk of MI}|\)

3%
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%)

88% with risk variant

Van Driest et al, Clin Pharmacol Therap. 2013
Multiplexed Genetic Testing can reduce testing too

53% more tests performed with reactive testing

Van Driest et al, Clin Pharmacol Therap. 2013
Initial analysis of Rx rates by CYP2C19

- 7405 PREDICT genotyped patients from 10/1/2010 to 6/30/2012:
  - 1620 with stent placed
  - “final” antiplatelet therapy identified at 90 days
Initial analysis of Rx rates by CYP2C19

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  - 1620 with stent placed
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Proportion prescribed drug within genotype group
## PREDICT: Cost to Patient
### Clopidogrel vs. Alternatives

<table>
<thead>
<tr>
<th>Antiplatelet Drug</th>
<th>Dose</th>
<th>Avg. Annual Retail Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>75 mg qd</td>
<td>$480.53</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>10 mg qd</td>
<td>$3365.52</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>90 mg qd</td>
<td>$1,736.79</td>
</tr>
</tbody>
</table>

**Maximum out-of-pocket cost of PREDICT test:** $420
eMERGE-PGx – Overall Goal

A multi-site test of targeted next-gen sequencing of 84 genes, validation, and EMR decision support to guide care in ~9,000 eMERGE patients.
Personalized medicine – not a new idea

The good physician treats the disease; the great physician treats the patient who has the disease.

Sir William Osler
The Teams

**Informatics**
- Josh Peterson
- Lisa Bastarache
- Kevin Johnson
- Hua Xu
- Brad Malin
- Dan Masys
- Wei-Qi Wei

**BioVU/SD**
- Melissa Basford
- Jill Pulley
- Erica Bowton
- Jay Cowan
- Sunny Wang
- Jenny Madison
- Sue Bradeen

**Medicine**
- Dan Roden
- Ellen Clayton
- Jessica Delaney
- Sara Van Driest
- Jonathan Mosley
- Andrea Ramirez
- Peter Weeke

**Genetics**
- Dana Crawford
- Marylyn Ritchie
- Todd Edwards

**Biostatistics**
- Jonathan Schildcrout
- Yaping Shi

**eMERGE Network**
- Children’s hospital of Philadelphia
- Boston Children’s/Cincinnati Children’s Hospitals
- Northwestern
- Marshfield Clinic
- Mayo Clinic
- Group Health/UW
- Mount Sinai
- Geisinger

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- NLM
- NIGMS
- NCI