eMERGE-II site report
Vanderbilt
29 June 2015
Vanderbilt activities – eMERGE II

- PGx implementation – locally and eMERGE-PGX
  - SCN5A/KCNH2 project
  - provider attitudes
- Phenotype contributions
- Methods development – MVtest
- PheWAS: development and current status
- CERC survey
  - developing sampling method
  - literature review
- Privacy: attack scenarios
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- PGx implementation – locally and eMERGE-PGx
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Pre-emptive pharmacogenetic testing at Vanderbilt

Since September 2010, 14,734 VU patients have had PREDICT testing.
Pre-emptive pharmacogenetic testing at Vanderbilt

Since September 2010, 14,734 VU patients have had PREDICT testing
Do interventional cardiologists change antiplatelet therapy in response to PREDICT testing?
PREDICT Provider survey

<table>
<thead>
<tr>
<th>Population</th>
<th>Clinician Survey (n=80; 56% response)</th>
<th>Clinician Interviews (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiology (51%), Internal Medicine (26%) and other (23%) attendings, nurse practitioners, or fellows</td>
<td>Cardiology and internal medicine attendings and fellows</td>
</tr>
<tr>
<td>Selection</td>
<td>Solicited 121 clinicians who ordered PREDICT testing</td>
<td>Stratified sample from low, medium, and high volume PREDICT users</td>
</tr>
<tr>
<td>Format</td>
<td>53 item REDCap survey addressing attitudes, satisfaction, and perceived clinical utility</td>
<td>Semi-structured 45 minute interview</td>
</tr>
<tr>
<td>Analysis</td>
<td>Descriptive</td>
<td>Recorded, transcribed and organized into qualitative themes (Grounded Theory)</td>
</tr>
</tbody>
</table>
PREDICT Provider Survey results overview

- Majority of clinicians (92%) favor immediate, active notification when a clinically significant drug-genome interaction is present.
- For knowledge sources, standards-setting organizations and summaries of the literature were more trusted than 3rd party laboratory sources.
- Clinicians were divided on which provider was responsible for acting on a result when a prescription change was indicated (see figure).
Long Term Responsibility

“I think it's going to be important to come up with good processes to educate referring physicians as well as ordering physicians and specialists on how to handle this information. Who do you need to notify? Who's responsible for acting on the information?”

“It’s important to me to know the [consequences] of a cardiologist ordering a test that has implications when the patient is prescribed Azathioprine, or an SSRI, or a non-cardiac drug.”
Genotype representation

Which genotyping result format is most clear and useful to you?

*1B No Call; *11/*13 No Call; *3 HET; *5 HET  3%
*1/*5                                           3%
1 copy of *5 risk allele (*1B No Call;*11/*13 No Call;*3 HET; *5 HET)  20%
1 copy of *5 risk allele                        24%
No reporting of specific genotype result is necessary  50%
## VU contribution to eMERGE-II phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>VU Role</th>
<th>Case / Cntl</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. Diff</em></td>
<td>2°</td>
<td>941/1720</td>
<td>100/100</td>
</tr>
<tr>
<td><em>AAA</em></td>
<td>2°</td>
<td>38/152</td>
<td>100%</td>
</tr>
<tr>
<td><em>VTE</em></td>
<td>2°</td>
<td>341/7476</td>
<td>90%</td>
</tr>
<tr>
<td><em>Oc. HTN</em></td>
<td>network</td>
<td>26/271</td>
<td>100/92</td>
</tr>
<tr>
<td><em>Diverticulosis</em></td>
<td>2°</td>
<td>802/558</td>
<td>88%</td>
</tr>
<tr>
<td><em>ACE-I Cough</em></td>
<td>1°</td>
<td>1055/1385</td>
<td>100/100</td>
</tr>
<tr>
<td><em>Glaucoma</em></td>
<td>network</td>
<td>131/348</td>
<td></td>
</tr>
<tr>
<td><em>Zoster</em></td>
<td>2°</td>
<td>198/3910</td>
<td>96/100</td>
</tr>
<tr>
<td><em>Ext. Obesity</em></td>
<td>network</td>
<td>428/1741</td>
<td></td>
</tr>
<tr>
<td><em>Card. Resp. Fitness</em></td>
<td>network</td>
<td>186/na</td>
<td></td>
</tr>
<tr>
<td><em>DILI</em></td>
<td>network</td>
<td>1? / many</td>
<td></td>
</tr>
<tr>
<td><em>Heart Failure</em></td>
<td>network</td>
<td>1029/420</td>
<td></td>
</tr>
<tr>
<td><em>Asthma</em></td>
<td>2°</td>
<td>326/1336</td>
<td></td>
</tr>
<tr>
<td><em>Child Obesity</em></td>
<td>2°</td>
<td>4/4</td>
<td>99/98</td>
</tr>
<tr>
<td><em>MACE-Statins</em></td>
<td>1°</td>
<td>937/829</td>
<td>96 (case)</td>
</tr>
<tr>
<td><em>AMD</em></td>
<td>network</td>
<td>149 / 7424</td>
<td></td>
</tr>
<tr>
<td><em>Colon Polyps</em></td>
<td>network</td>
<td>630 / 2114</td>
<td></td>
</tr>
<tr>
<td><em>Autism</em></td>
<td>network</td>
<td>23/717</td>
<td></td>
</tr>
<tr>
<td><em>Atop. Derm.</em></td>
<td>network</td>
<td>72/3596</td>
<td></td>
</tr>
<tr>
<td><em>CAAD</em></td>
<td>network</td>
<td>128/4571</td>
<td></td>
</tr>
<tr>
<td><em>BPH</em></td>
<td>1°</td>
<td>415/446</td>
<td>100/100</td>
</tr>
<tr>
<td><em>GERD</em></td>
<td>network</td>
<td>1642/2862</td>
<td></td>
</tr>
<tr>
<td><em>CKD</em></td>
<td>network</td>
<td>4348/513</td>
<td></td>
</tr>
<tr>
<td><em>caMRSA</em></td>
<td>network</td>
<td>262/2313</td>
<td></td>
</tr>
<tr>
<td><em>ADHD</em></td>
<td>network</td>
<td>58/3088</td>
<td></td>
</tr>
<tr>
<td><em>fibroids</em></td>
<td>1°</td>
<td>2298 / 2495</td>
<td>96%</td>
</tr>
</tbody>
</table>
SNP variants associated with ACEi induced cough

- ACE-inhibitor induced cough
  - Most common side effect (~10%)
  - More common in women and Asian populations

- Methods
  - GWAS
    - Discovery set:
      - eMERGE (1,595 cases and 5,485 controls)
    - Replication sets:
      - eMERGE (157 cases and 769 controls)
      - GoDARTS (710 cases and 3,599 controls)
Intronic SNPs in *KCNIP4* are associated with ace-induced cough.
Intronic SNPs in *KCNIP4* are associated with ace-induced cough
Fibroid GWAS

• Six eMERGE Network sites (N=10,227)
  • AA 1,354 cases and 1,419 controls
  • EA 2,843 cases and 4,611 controls
• Imputation:
  • IMPUTE 2 with 1000 Genomes October 2014 build 37
• Association
  • Adjusted for up to 5 PCs
  • SNPTest v2.4.1
• Fixed effects meta-analysis with Metal
Transethnic Fibroid GWAS

Common Variants (MAF ≥0.05)
MACE while on statins

- Preliminary results in 1,392 MACE cases (373 AMI) and 3,561 controls
- New genotyping at VU and Marshfield through PGRN; now in analysis: 5862 samples (1733 cases)
PheWAS: the initial eMERGE result

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

63 new associations, mostly with skin phenotypes
GWAS of T2D

Wellcome Trust Case Control Consortium (*Nature*, 2007)

PheWAS on *FTO* intron

unadjusted for BMI

adjusted for BMI
PheWAS on max(WBC count)
Genetics of rheumatoid arthritis contributes to biology and drug discovery

Okada et al., *Nature* 2013

- >100,000 cases and controls from RA studies and biobanks, multiple ethnicities
- 101 RA loci $\rightarrow$ 98 candidate genes
PheWAS of all RA risk variants

1. Calculate Genetic Risk Score (GRS) using 101 loci in eMERGE dataset
2. Look for phenotypes associated via GRS (adjusted for Age, Sex, Principal Components)

Genetic Risk Score = \sum_{i=1}^{101} SNP_i \text{weight}_i
PheWAS of RA risk variants, optimizing weights and combinations for each SNP and disease.
Network analysis of PheWAS on RA risk SNPs
Neanderthal PheWAS

- ~1.5% of the genome of non-African individuals is inherited from admixture with Neanderthals.
- Neanderthal alleles identified in the eMERGE imputed set.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>SNP</th>
<th>Flanking Gene(s)</th>
<th>Discovery (E1) Odds Ratio</th>
<th>Replication (E2) Odds Ratio</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercoagulable state</td>
<td>rs3917862</td>
<td>SELP</td>
<td>3.32</td>
<td>9.9E-07</td>
<td>3.00</td>
<td>5.0E-10</td>
</tr>
<tr>
<td>Protein-calorie malnutrition</td>
<td>rs12049593</td>
<td>SLC35F3</td>
<td>1.77</td>
<td>2.0E-06</td>
<td>1.63</td>
<td>5.5E-05</td>
</tr>
<tr>
<td>Symptoms involving urinary system</td>
<td>rs11030043</td>
<td>RHOG, STIM1</td>
<td>1.76</td>
<td>7.4E-06</td>
<td>1.65</td>
<td>4.3E-02</td>
</tr>
<tr>
<td>Tobacco use disorder</td>
<td>rs901033</td>
<td>SLC6A11</td>
<td>2.19</td>
<td>1.7E-05</td>
<td>1.75</td>
<td>7.9E-04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phenotype (Code)</th>
<th>Discovery (E1) Risk Explained</th>
<th>Replication (E2) Risk Explained</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction (411.2)</td>
<td>1.39%</td>
<td>0.13%</td>
<td>1.7E-03</td>
<td>0.373</td>
</tr>
<tr>
<td>Depression (296.2)</td>
<td>2.03%</td>
<td>1.06%</td>
<td>2.3E-03</td>
<td>0.031</td>
</tr>
<tr>
<td>Corns and callosities (700)</td>
<td>1.26%</td>
<td>0.21%</td>
<td>3.5E-03</td>
<td>0.281</td>
</tr>
<tr>
<td>Mood disorders (296)</td>
<td>1.11%</td>
<td>0.68%</td>
<td>9.1E-03</td>
<td>0.029</td>
</tr>
<tr>
<td>Overweight (278)</td>
<td>0.60%</td>
<td>0.23%</td>
<td>0.037</td>
<td>0.241</td>
</tr>
<tr>
<td>Seborrheic keratosis (702.2)</td>
<td>0.77%</td>
<td>0.41%</td>
<td>0.038</td>
<td>0.131</td>
</tr>
<tr>
<td>Coronary atherosclerosis (411.4)</td>
<td>0.68%</td>
<td>0.34%</td>
<td>0.040</td>
<td>0.153</td>
</tr>
<tr>
<td>Upper respiratory infections (465)</td>
<td>0.70%</td>
<td>0.34%</td>
<td>0.043</td>
<td>0.176</td>
</tr>
</tbody>
</table>
Neanderthal PheWAS

$N = 60, P = 0.017$
Ongoing eMERGE II Projects

- Phenotypes:
  - BPH – completing analyses
  - C.Diff. – Gathering additional cohorts
  - Fibroids – Completing Analyses and Publication

- PheWAS:
  - RA GRS network analysis
  - Using NLP to refine phenome definition
  - Association with other-than-genomics data
  - Variants aggregated by gene / pathway

- Clinical Outcomes:
  - Clopidogrel outcomes

- Methods:
  - Mvtest - other quantitative traits:

- Privacy:
  - attack liabilities
The Teams

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

The Vanderbilt Genome-Electronic Records Project