Review of articles describing clinical implementation of pharmacogenetics based on preemptive genotyping

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Articles, that have been reviewed

List of reviewed articles includes:


First two articles from Vanderbilt University Medical Center - VUMC.
Objectives

- Preemptive Genotyping
- Evaluation of number of AEs, that might have been prevented using a preemptive pharmacogenetic genotyping strategy
- Reporting of the results of the preemptive integration under the described programs
52,942 medical home individuals were observed during 5 years, which:

- Were receiving primary care at VUMC
- Had completed three outpatient visits in a 2-year time frame within primary care, nephrology, cardiology, or diabetes clinics
Six well-characterized medications with severe AEs (abacavir (skin/mucosal hypersensitivity), azathioprine (myelosuppression), clopidogrel (lack of efficacy to prevent major cardiovascular events, i.e., myocardial infarction, stroke, or death), simvastatin (myopathy), tamoxifen (breast cancer recurrence), and warfarin (bleeding)).

- Prescription records were collected (from January 2005 to June 2010)
- Then the list of most relevant medications has been extracted from prescriptions
First article. Data, needed for evaluation of adverse events number, that could have been prevented

Estimated:

- Number of medication exposures:
  5-year medication ($med$) exposure probability ($pr(med)$) was estimated used the Kaplan-Meier product limit estimator of cumulative incidence. Then the expected number of $med$ exposures was estimated as $N_{med} = N \times pr(med)$.

From literature:

- Variant allele and genotypes frequencies (as a genetic risk strata): $pr(G = G\mid med)$, where $G = g$ and $g = \{0, 1, or 2\}$ denotes mono- and heterozygous.
- Overall adverse event (AE) rates
- AEs excess risk estimates (including both drug toxicities and efficacy failures): OR, HR, RR
First article. Evaluation of adverse events number, that could have been prevented

We define:

- \( pr(G = G|med) \) - a stratum \( g \) prevalence (probability to see it in population) for those receiving medication \( med \), respectively
- \( pr(AE|G = g, med) \) the AE probability (i.e., risk) in stratum \( g \) for those receiving medication \( med \), respectively
- \( ARD_{med,g} = pr(AE|G = g, med) - pr(AE|G = 0, med) \) reflects the absolute risk difference between risk stratum \( G = g \) and \( G = 0 \)

Then, the number of AEs prevented \( (NP_{med,g,p}) \) for those in stratum \( G = g \) on medication \( med \) is given by formula:

\[
NP_{med,g,p} = N_{med} \cdot pr(G = G|med) \cdot p \cdot ARD_{med,g}
\]

where \( 0 \leq p \leq 1 \) to be the proportionate risk reduction in \( ARD_{med,g} \) in the presence of an intervention on the high risk.
383 events (95% CI, 212-552) among a cohort of 52,942 medical home patients at VUMC could have been prevented, based on 5-years follow up period and for six medications.
The PREDICT started in September 2010. For raising awareness of the PREDICT and getting of feedback:

- Information related to PREDICT has been included in the standard "Consent to Treatment" forms that all patients sign upon registration.
- The main point and design of PREDICT were discussed with patients verbally, the conversation was documented, preferences were recorded, and brochures were provided.
Clopidogrel - medication used in antiplatelet therapy after placement of cardiovascular stents. The choice has been done based on evidences:

- In 2009, clopidogrel was the third most commonly prescribed drug in the United States
- At the same time several single centers reported that individuals homozygous for CYP2C19*2, a loss-of-function allele, displayed increased rates of adverse cardiovascular events while on clopidogrel therapy after coronary stenting.
- More recently, results of different meta-analyses have confirmed this risk and have extended it to include individuals who are heterozygous (termed CYP2C19*1/*2) for this variant.
Based on results of 2008, clopidogrel was ultimately prescribed to 42.5% patients, who underwent coronary angiography at VUMC:

- The initial group of patients targeted for preemptive genotyping were those scheduled for coronary arteriography, before any decision to prescribe clopidogrel. So, genotyping was ordered in 63% out of 3,449 patients, who had undergone heart catheterization at 1 August 2011. (2172 patients)
Second article, main steps toward implementation

- Generating of genotype results.
- Storing the results in a database (which resides at the VUMC data center behind its firewall and are not accessible by patients or providers), where the approved for clinical implementation ("actionable") genotypes are separated from non-approved genetic data as following:
  - Approved genotypes are converted into a standard notation and interpretation (e.g., CYP2C19*2, "Poor Metabolizer: Reduced anti-platelet effect")
  - Non-approved (with low call rate of genotyping or missing data..) are kept in database behind firewall until appropriate and are linked to the patient
- Approved, notated and interpreted data are recorded into the EMR (electronic medical record) as a molecular diagnostic laboratory result, and displayed within a "Drug-Genome Interaction" section of the patient summary page of the EMR
Second article, interface of Drug-Genome Interaction section of the patient summary page of the EMR

<table>
<thead>
<tr>
<th>General Information:</th>
<th>Adverse and Allergic Drug Reactions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP:</td>
<td>No known allergies</td>
</tr>
<tr>
<td>Significant Medical Diagnoses and Conditions:</td>
<td>Drug Genome Interactions: (03/28/11 13:00)</td>
</tr>
<tr>
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<td>CYP2C19 sensitivity; POOR METABOLIZER, REDUCED ANTI-PLATELET EFFECT - gene: CYP2C19 - gene result: &quot;2/2/2&quot;</td>
</tr>
<tr>
<td></td>
<td>Medications: prepare to print print and give pt Show Hx of medications</td>
</tr>
<tr>
<td></td>
<td>Drug/Herb Interactions: Utic 40mg orally once daily</td>
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<tr>
<td></td>
<td>E.C. Aspirin 325mg orally once daily</td>
</tr>
<tr>
<td></td>
<td>Twice daily 0.4mg, one tab sitting at first sign of chest pain, every five minutes up to 3 doses. If after</td>
</tr>
</tbody>
</table>

**Clopidogrel Poor Metabolizer Rules**

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 rates of stent thrombosis/other cardiovascular events.

**Treatment modification is recommended if not contraindicated:**

- Describe prasugrel (EFFIENT) 10mg daily and stop clopidogrel (Plavix) therapy.
- Due to increased risk of bleeding compared to clopidogrel, 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) 75 mg daily, startdate, 10 days
- Maintain requested daily dose of clopidogrel (PLAVIX) 75 mg daily, startdate, 10 days

If not using prasugrel, please select a reason:

- Contraindicated for prasugrel
- Potential side effects
- Patent options for clopidogrel
- Other (Specify)

Click here for more information:

**Presentation of genetic test results in an electronic medical record and clinical decision-support guidance within the order entry system.**
Underlying idea the same but this time 12 high-risk drugs (that are coupled to considered four genes: TPMT, CYP2D6, SLCO1B1, and CYP2C19) and 55 clinical decision support rules were implemented.
QUESTIONS ?