A Pilot Study of the Incidence of Exposure to Drugs for which Pre-emptive Pharmacogenomic Testing Is Available

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Study significance 1

- Adverse drug reactions and ineffective drug therapy are major issues in modern healthcare systems.

- Pharmacogenomic (PGx) testing could help to reduce the occurrence of these events by individualizing drug therapy.

- Workflow implementation issues and economic considerations are major barriers to a widespread adoption of PGx testing.
Pre-emptive PGx testing could help to overcome these barriers

Studies on potential return on investment for pre-emptive PGx testing are promising but rare and limited to localized settings
Objectives

- Derive data on incident use of PGx drugs

- Value proposition
  - The data could be used to evaluate utility of testing panels
  - The data could be combined with data on ADR risk and costs
    - enabling cost-effectiveness/cost-benefit analyses to justify pre-emptive pharmacogenomics testing by large healthcare organisations or payers
Methods - Data sources 1

- Compiled list of PGx drugs
  - i.e., drugs with clinical pharmacogenomic guidelines
  - Two sources
    - The Clinical Pharmacogenomics Implementation Consortium (CPIC)
    - The Dutch Pharmacogenetics Working Group (DPWG)
Example CPIC guideline for clopidogrel
“The CPIC Dosing Guideline for clopidogrel recommends an alternative antiplatelet therapy (e.g., prasugrel, ticagrelor) for CYP2C19 poor or intermediate metabolizers if there is no contraindication.”  https://www.pharmgkb.org/guideline/PA166104948

Example DPWG guideline for escitalopram
For CYP2C19 ultrarapid metabolizers, monitor escitalopram plasma concentration and titrate dose to a maximum of 150% in response to efficacy and adverse drug event, or select alternative drug.  https://www.pharmgkb.org/guideline/PA166104975
Methods - Data sources 3

- **Patient data sources (all administrative claims)**
  - Truven MarketScan® Commercial Claims and Encounters (CCAE) Database
    - a privately-insured population of over 100 million patients from multiple larger employers/payers in the US covering the years 2003 to 2013
  - Truven MarketScan® Multi-state Medicaid
    - Over 15 million Medicaid enrollees from multiple states in the US covering the years 2002 to 2012
  - Truven MarketScan® Medicare Supplemental Beneficiaries
    - 8 million US retirees with Medicare supplemental insurance paid by employers covering 2003 to 2013
Methods - Data sources 4

- IMEDS Research Lab
  - OMOP Common Data Model and Standard Vocabulary Version 4
  - queried using SQL Workbench/J (build 116) “RedShift” profile
Methods - Study design 1

- Cross-sectional study of drug utilization across each dataset

- Inclusion criteria
  - Incident prescriptions (no prescriptions of the drug prior to 1/1/2009)

- Exclusion criteria
  - Topical preparations of PGx drugs
Methods - Study design 2

- **Age ranges**
  - CCAE and Medicaid: 0-13, 14-39, 40-64
  - Medicare: >= 65

- **Scenarios**
  - Pre-emptive Testing
    - Genetic test would be conducted at the start of the defined time window
  - Reactive pre-emptive Testing
    - Genetic test would be conducted at time of first incident use of PGx drug
Results 1

- Compiled list of PGx drugs
  - 61 drug substances
  - 73 substance-gene interaction pairs
    - 25 from CPIC and 62 from DPWG

- Core List
  - PGx drugs associated with genes that are typically covered by common assays (e.g. CYP2C19, CYP2D6)
### Results 2

- A sample of the **core list** - drugs for which CPIC\(^a\) or DPWG\(^b\) guidelines are currently available AND the genes are commonly tested

<table>
<thead>
<tr>
<th>Gene</th>
<th>Substances associated with gene in pharmacogenomic guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core list</strong></td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>amitriptyline(^a, b), clomipramine(^a, b), clopidogrel(^a, b), desipramine(^a), doxepin(^b), imipramine(^a, b), nortriptyline(^a, b), trimipramine(^a), citalopram(^b), escitalopram(^b), esomeprazole(^b), lansoprazole(^b), moclobemide(^b), omeprazole(^b), pantoprazole(^b), rabeprazole(^b), sertraline(^b), voriconazole(^b)</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>warfarin(^a), acenocoumarol(^b), glibenclamide(^b), gliclazide(^b), glimepiride(^b), phenprocoumon(^b), phenytoin(^b), tolbutamide(^b)</td>
</tr>
</tbody>
</table>
Results 3

- 89 635 500 patient records
  - 55.3% associated with female patients
- Patients receiving two or more PGx drugs
  (Pre-emptive Testing)

<table>
<thead>
<tr>
<th>Age</th>
<th>CCAE</th>
<th>Medicaid</th>
<th>Medicare</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-13</td>
<td>0.77%</td>
<td>1.40%</td>
<td>N/A</td>
</tr>
<tr>
<td>14-39</td>
<td>9.94%</td>
<td>14.71%</td>
<td>N/A</td>
</tr>
<tr>
<td>40-64</td>
<td>13.70%</td>
<td>32.20%</td>
<td>N/A</td>
</tr>
<tr>
<td>&gt;=65</td>
<td>N/A</td>
<td>N/A</td>
<td>26.80%</td>
</tr>
</tbody>
</table>
Results 4

- Patients receiving two or more PGx drugs (Reactive pre-emptive Testing)

<table>
<thead>
<tr>
<th>Age</th>
<th>CCAE</th>
<th>Medicaid</th>
<th>Medicare</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-13</td>
<td>9.60%</td>
<td>12.10%</td>
<td>N/A</td>
</tr>
<tr>
<td>14-39</td>
<td>31.10%</td>
<td>37.90%</td>
<td>N/A</td>
</tr>
<tr>
<td>40-64</td>
<td>43.30%</td>
<td>59.00%</td>
<td>N/A</td>
</tr>
<tr>
<td>&gt;=65</td>
<td>N/A</td>
<td>N/A</td>
<td>54.60%</td>
</tr>
</tbody>
</table>
Results 5

- **Genes excluded from core list:**
  - F5 (ethinyl estradiol – thrombophilia risk)
  - HLA-B (severe cutaneous ADRs to several drugs)
  - IFNL3 (predictor of response to hepatitis C therapy)

- **Inclusion of associated drugs significantly increases incident use of >= 2 drugs in 14-64 age ranges**
  - 14-39: mainly caused by first prescriptions for ethinyl estradiol
Future work 1

- Generate further statistics on genes associated with PGx medications
  - Examine risk factors for exposure
  - Correlations related to exposure
    - E.g., to a second PGx drug once given a first

- Extend the study to regions outside the U.S.
  - From health systems that have very different patient populations from the current study
Future work 2

- A new research protocol to extend the study
  - The Observational Health Data Sciences and Informatics collaborative research network
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Discussion