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

Richard D. Boyce[1]
Kathrin Blagec[2]
Matthias Samwald[2]

[1]Department of Biomedical Informatics, University of Pittsburgh
[2]Section for Medical Expert and Knowledge-Based Systems Medical University of Vienna

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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**

Study significance 2

- **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)

Methods - Data sources 2

- **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**
  - Time window: 1/1/2009 – 12/31/2012
  - 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

Gene	Substances associated with gene in pharmacogenomic guidelines
Core list	
CYP2C19	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]
CYP2C9	warfarin[a], acenocoumarol[b], glibenclamide[b], gliclazide[b], glimepiride[b], phenprocoumon[b], phenytoin[b], tolbutamide[b]

Results 3

- **89 635 500 patient records**
  - 55.3% associated with female patients
- **Patients receiving two or more PGx drugs**

(Pre-emptive Testing)

Age	CCAE	Medicaid	Medicare
0-13	0.77%	1.40%	N/A
14-39	9.94%	14.71%	N/A
40-64	13.70%	32.20%	N/A
>=65	N/A	N/A	26.80%

Results 4

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

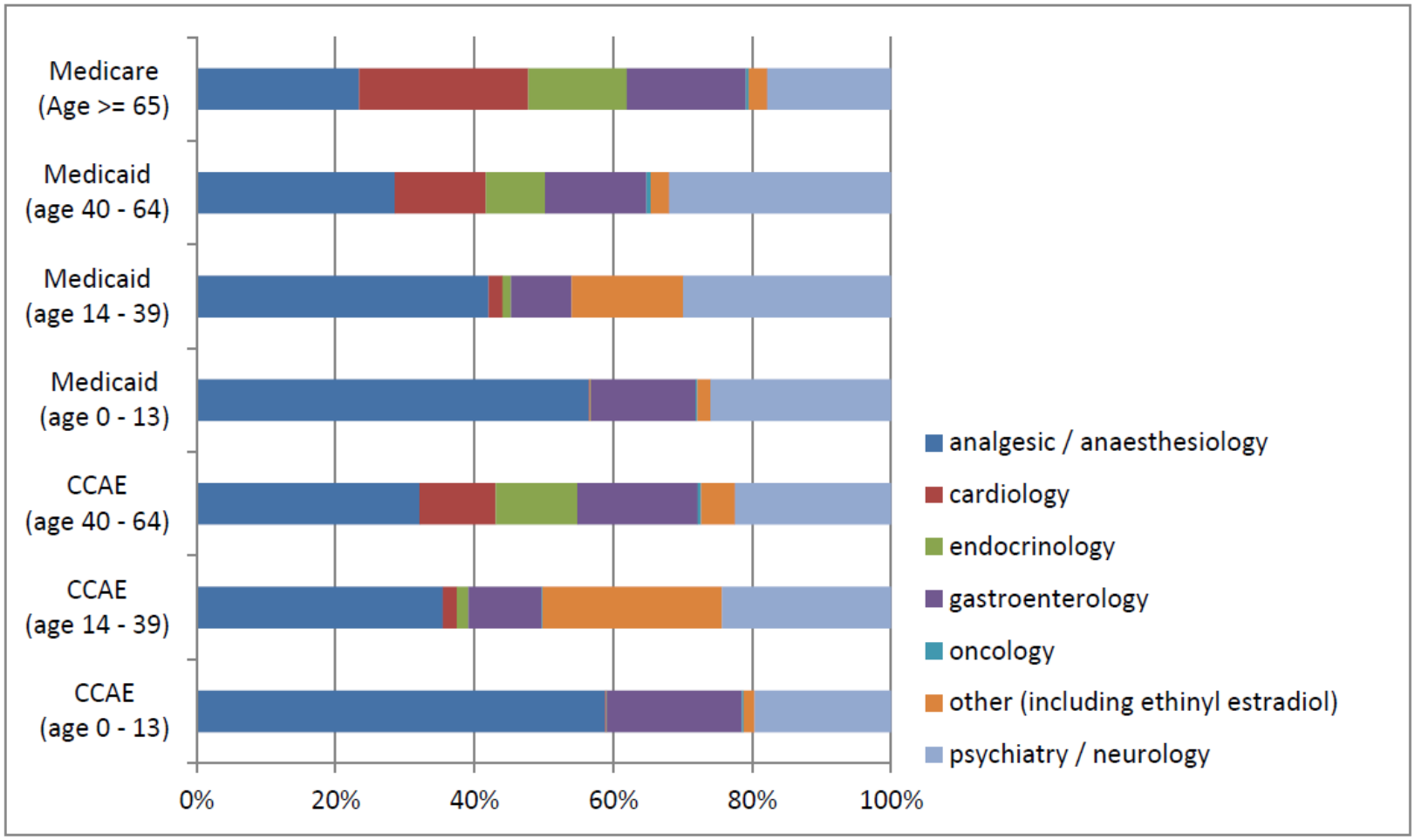
Age	CCAE	Medicaid	Medicare
0-13	9.60%	12.10%	N/A
14-39	31.10%	37.90%	N/A
40-64	43.30%	59.00%	N/A
>=65	N/A	N/A	54.60%

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

Results 6


Medicare (Age >= 65)
Medicaid (age 40 - 64)
Medicaid (age 14 - 39)
Medicaid (age 0 - 13)
CCAE (age 40 - 64)
CCAE (age 14 - 39)
CCAE (age 0 - 13)
0%
20%
40%
60%
80%
100%
analgesic / anaesthesiology
cardiology
endocrinology
gastroenterology
oncology
other (including ethinyl estradiol)
psychiatry / neurology

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
    - http://purl.org/net/drug-interaction-knowledge-base/OHDSI-PGx-incidence-protocol

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Discussion