Red Light, Green Light!
Precision Pediatrics and the Electronic Health Record

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Precision Pediatrics and the Electronic Health Record

Road Map

• What is Precision Pediatrics?
• Some Examples from Pharmacogenomics
• Leveraging EHR Data for Children
Which treatment is best for this problem?
Which treatment is best for this patient?

Some reasons for variable drug effects:

- Age, sex
- Ancestry
- Drug interactions
- Environment
- Diagnosis
- Genetics
  - Variable drug levels
  - Altered responsiveness
What about Pediatrics?

"Children are not small adults" - Unique (patho)physiology - Unique treatments - Unique responses
Precision Pediatrics

• Easier
  • Healthy organs = large genetic effect size
  • Dosing flexibility
  • Titration to effect
  • “Culture of extrapolation”

• Harder
  • Healthy organs = fewer hard outcomes
  • Small sample size (and you need BIGGER)
  • Titration to effect
  • “Culture of paternalistic (and maternalistic) providers”
Road Map

• What is Precision Pediatrics?
• Some Examples from Pharmacogenomics
• Leveraging EHR Data for Children
Personalized Antiplatelet Tx: A Precision Medicine Success Story

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

**Primary override reason:**
- Contraindicated for prasugrel or ticagrelor
- Potential side effects
- Provider/Patient opts for clopidogrel
- Cost

Personalized Antiplatelet Tx: A Precision Medicine Success Story

Cavallari 2016, AHA
What about Children?

• Is this DGI Relevant to Children?
  • Children are (rarely) prescribed clopidogrel
  • CYP2C19 is expressed in young children
  • There are no studies...

• CPIC recommendation

At the time of the development of this recommendation, there are no data available on the possible role of CYP2C19 in clopidogrel response in pediatric patient populations; however, there is no reason to suspect that CYP2C19 variant alleles would affect clopidogrel metabolism differently in children as compared with adults.

https://www.pharmgkb.org/chemical/PA449053
What about Children?

• Decision Support?

If not otherwise contraindicated:

☐ Prescribe prasugrel (Effient) 10 mg daily

Prasugrel should not be given to patients:
• history of stroke or transient ischemic attack
• >= 75 years of age
• with body weight < 60 kg

☐ Prescribe ticagrelor (Brilinta) 90 mg twice daily

Ticagrelor should not be given to patients:
• history of severe hepatic impairment
• intracranial bleed

☑ Continue with clopidogrel (Plavix) prescription

Primary override reason:
☐ Contraindicated for prasugrel or ticagrelor
☐ Potential side effects
☐ Provider/Patient opts for clopidogrel
☐ Cost
Current Drug-Gene Interactions

Clopidogrel – CYP2C19
Warfarin – CYP2C9 and VKORC1
Simvastatin – SLCO1B1
Thiopurine Drugs – TPMT
Tacrolimus – CYP3A5
What about Warfarin in Children?

- Children are (rarely) prescribed warfarin
  - New alternative agents not used in pediatrics
  - There are studies
## What about Warfarin in Children?

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>N</th>
<th>Ethnicities</th>
<th>Ages (years) (mean)</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nowak et al (2010)</td>
<td>Prospective Cohort</td>
<td>59 (34 on Warfarin)</td>
<td>100% White</td>
<td>1-19 (15)</td>
<td>Age accounts for 28.3% of dose variability; no role for genotype</td>
</tr>
<tr>
<td>Kato et al (2011)</td>
<td>Retrospective Cohort</td>
<td>48</td>
<td>100% Japanese</td>
<td>0.5-19 yo (6.6)</td>
<td>VKORC1 is a major determinant of required warfarin dose; CYP2C9 could not be evaluated</td>
</tr>
<tr>
<td>Biss et al (Blood 2012)</td>
<td>Cross-sectional</td>
<td>120</td>
<td>75.8% White, 8.3% Indian, 5% Black, 5% Asian, 5.8% Other</td>
<td>1-18 (11)</td>
<td>VKORC1, CYP2C9, height, and indication account for 72.4% of dose variability; IWPC algorithm consistently overestimates necessary dose</td>
</tr>
<tr>
<td>Moreau et al (Blood 2012)</td>
<td>Retrospective Cohort</td>
<td>118 (83 on warfarin)</td>
<td>&gt;90% White</td>
<td>0.25-18 (8.4)</td>
<td>VKORC1 accounts for 18.2% of dose variability, CYP2C9 2%, and height 48.1%</td>
</tr>
<tr>
<td>Nguyen et al (Pediatric Cardiology 2012)</td>
<td>Prospective Cohort</td>
<td>37 (all pts with heart disease)</td>
<td>73% White, 18.9% Black, 8.1% Asian</td>
<td>1.8-18.6 (9.6)</td>
<td>VKORC1 is a major determinant of required warfarin dose; with CYP2C9 only accounting for 5% of variability; age, height, and goal INR also contribute</td>
</tr>
<tr>
<td>Vear et al (Br J Haematol 2014)</td>
<td>Retrospective Cohort</td>
<td>100</td>
<td>85% White, 8% Black</td>
<td>1-20 (12.39)</td>
<td>Age, CYP2C9 genotype, VKORC1 genotype and age:VKORC1 interaction accounted for 53% of warfarin dose variability</td>
</tr>
</tbody>
</table>
Warfarin Dose Calculator?

Warfarin Recommended Initial Dosing
This patient has been tested for CYP2C9 and VKORC1 genetic variants that can affect a patient's warfarin dosing requirements. The following dosing algorithm uses genetic and other patient information to estimate a weekly warfarin dose. This dosing recommendation ONLY applies to NEW starts of warfarin. If the patient has previously taken a stable dose of warfarin, please disregard this dosing recommendation.

- Age: 25
- Weight (kg): 86.2
- Height (cm): 188.0
- Genetic Variants: vkorc1 a/g; cyp2c9 *3/*3;
- Is the patient currently taking amiodarone? No
- Is the patient currently taking an inducer (phenytoin, rifampin, carbamazepine)? Yes

Recommended WEEKLY starting dose of warfarin: 20.9 mg/week
The DAILY equivalent of this recommended starting dose is 3.0 mg/day.
Help me decide the tablet size and number of tablets per day
Current Drug-Gene Interactions

Clopidogrel – CYP2C19
Warfarin – CYP2C9 and VKORC1
Simvastatin – SLCO1B1
Thiopurine Drugs – TPMT
Tacrolimus – CYP3A5
Simvastatin

• Children are (rarely) prescribed Simvastatin
• The SLCO1B1 drug-gene-interaction...
  • Predicts myopathy, which is very rare in children
  • Existing data may suggest the opposite direction of effect!
• CPIC recommendation

"At the time of this writing, there are no data available regarding SLCO1B1 genotype effects on simvastatin response or myopathy in pediatric patient populations, although there is no reason to suspect that the polymorphisms in SLCO1B1 will affect simvastatin’s metabolism differently in children compared to adults."
Current Drug-Gene Interactions

Clopidogrel – CYP2C19
Warfarin – CYP2C9 and VKORC1
Simvastatin – SLCO1B1

Thiopurine Drugs – TPMT
Tacrolimus – CYP3A5
Pediatric Application: Codeine

Pharmacogenetics for Safe Codeine Use in Sickle Cell Disease

Roseann S. Gammal, PharmD, Kristine R. Crews, PharmD, Cyrine E. Haidar, PharmD, James M. Hoffman, PharmD, MS, Donald K. Baker, PharmD, MBA, Patricia J. Barker, PharmD, Jeremie H. Estepp, MD, Deqing Pei, MS, Ulrich Broeckel, MD, Winfred Wang, MD, Mitchell J. Weiss, MD, PhD, Mary V. Relling, PharmD, Jane Hankins, MD, MS

**Pediatric Application: Codeine**

<table>
<thead>
<tr>
<th>CYP2D6 phenotype</th>
<th>n</th>
<th>Patients for Whom a Codeine-Containing Analgesic Was Dispensed, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-risk phenotypes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultra-rapid metabolizer</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Possible ultra-rapid metabolizer</td>
<td>25</td>
<td>1(^a) (4)</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td><strong>Non–high-risk phenotypes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>488</td>
<td>161 (33)</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>42</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Possible intermediate metabolizer</td>
<td>13</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Unknown risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>25</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

\(^a\) Patient had a documented history of tolerating codeine well in the past.
Road Map

• What is Precision Pediatrics?
• Some Examples from Pharmacogenomics
• Leveraging EHR Data for Children
Acute Kidney Injury in Pediatric Patients

- Acute Kidney Injury (AKI)
  - 1.5-fold or 0.3 mg/dL increase in creatinine
  - >5% of children on Wards
  - >25% of children in PICU
  - Increased morbidity, mortality and length of stay
- Many Pediatric Patients Are Unscreened

Wouldn’t it be nice…

- To have some idea of which patients are at risk for AKI, so we can target screening efforts?
  - Screening = Checking Serum Creatinine
  - Targeted screening has reduced severity at other Children’s Hospitals
- Building the model using EHR-derived variables should enable implementation

Goldstein et al, *Pediatrics* 2013
Downes et al, *J Cyst Fibros* 2014
Methods Overview

Generate Dataset

Predictive Modeling

Model Validation

Demonstrate Clinical Utility

• EMR Data Extraction from Research Derivative

• Selection of Covariates

• Logistic Regression

• Internal Validation by Bootstrapping

• External Validation in Independent Cohort

• (Randomized Trial)

Wang et al, In Review
Acute Kidney Injury Cohort

Development Cohort: 2011-2012

All Children’s Hospital Admissions (N=18,204)

Excluded (age or CKD, N=1311)

Admissions (N=16,893)

ICU (N=2979)

SCr Measured (N=1359)

No AKI (N=541) AKI (N=818)

Non-ICU (N=13,914)

SCr Measured (N=2374)

No AKI (N=1615) AKI (N=759)
Selection of Covariates

- 29 Covariates Considered
- Criteria
  - Informative
  - Non-missing
  - Independent
  - Available in Real-Time
Variables Associated with AKI

- Age at admission: 15 years vs. 3 years
- High risk nephrotoxins: Increase per 1 additional
- Moderate risk nephrotoxins: Increase per 1 additional
- Total medications: Increase per 1 additional
- Minimum platelet count: 278 vs. 206x10^3/μL
- Median RDW: 13.5 vs. 13.2%
- Phosphorus: None checked vs. normal; High value vs. normal
- Transaminases: None checked vs. normal; High value vs. normal
- Minimum pH: 7.3 vs. 7.2
- Hypotension: Present vs. absent
Predictive Models for AKI

The linear predictor, $X\beta$, for risk of AKI in ICU patients estimated from logistic model is given by:

$$\text{Prob}(\text{AKI} = 1) = 1/(1 + \exp(-X\beta)), \text{ where}$$

$$X\beta = 33.23465$$

- $0.133488$(age of patient in years at time of admission)
- $+ 0.000665906$(age $- 0.3225188)^3 \{x_1 \text{ if age}>0.3225188, x_0 \text{ if not} \}$
- $- 0.0008929974$(age $- 4.298426)^3 \{x_1 \text{ if age}>4.298426, x_0 \text{ if not} \}$
- $+ 0.0002270168$(age $- 15.96222)^3 \{x_1 \text{ if age}>15.96222, x_0 \text{ if not} \}$
- $+ 0.09773457$(number of high risk nephrotoxins)
- $+ 0.7827242$(number of moderate nephrotoxins)
- $- 0.1203862$(total number of medications)
- $- 0.003730175$(minimum platelet count)
- $+ 7.159349\times 10^{-6}$(minimum platelet count $- 109.8)^3 \{x_1 \text{ if plt}>109.8, x_0 \text{ if not} \}$
- $- 2.518633\times 10^{-6}$(minimum platelet count $- 278)^3 \{x_1 \text{ if plt}>278, x_0 \text{ if not} \}$
- $+ 1.802698\times 10^{-6}$(minimum platelet count $- 344.8)^3 \{x_1 \text{ if plt}>344.8, x_0 \text{ if not} \}$
- $+ 0.2870502$(median RDW)
- $- 0.08475973$(median RDW $- 12.7)^3 \{x_1 \text{ if RDW}>12.7, x_0 \text{ if not} \}$
- $+ 0.11691$(median RDW $- 13.25)^3 \{x_1 \text{ if RDW}>13.25, x_0 \text{ if not} \}$
- $- 0.03215024$(median RDW $- 14.7)^3 \{x_1 \text{ if RDW}>14.7, x_0 \text{ if not} \}$
- $- 0.6062568\{x_1 \text{ if all Phosphorus below ULN; } x_0 \text{ if not} \}$
+ $1.045055\{x_1 \text{ if 1 or more Phosphorus above ULN, } x_0 \text{ if not} \}$
- $- 1.660279\{x_1 \text{ if all transaminases below ULN, } x_0 \text{ if not} \}$
- $- 0.5513197\{x_1 \text{ if 1 or more transaminases above ULN; } x_0 \text{ if not} \}$
- $- 4.796936$(minimum pH)
+ $10.15878$(minimum pH $- 7.09)^3 \{x_1 \text{ if pH}>7.09, x_0 \text{ if not} \}$
- $- 47.40766$(minimum pH $- 7.31)^3 \{x_1 \text{ if pH}>7.31, x_0 \text{ if not} \}$
+ $37.24888$(minimum pH $- 7.37)^3 \{x_1 \text{ if pH}>7.37, x_0 \text{ if not} \}$
+ $0.2708241\{x_1 \text{ if hypotension, } x_0 \text{ if not} \}$
AKI Predictive Models Perform Well in Internal Validation

ICU

Non-ICU

Actual Probability

Predicted Probability

Apparent
Bias-corrected
Ideal
Acute Kidney Injury Cohorts

Development Cohort: 2011-2012

All Children’s Hospital Admissions (N=18,204)

Excluded (age or CKD, N=1311)

Admissions (N=16,893)

ICU (N=2979)

Non-ICU (N=13,914)

SCr Measured (N=1359)

SCr Measured (N=2374)

No AKI (N=541) AKI (N=818) No AKI (N=1615) AKI (N=759)

Validation Cohort: 2013

All Children’s Hospital Admissions (N=11,059)

Excluded (age or CKD, N=321)

Admissions (N=10,738)

ICU (N=1665)

Non-ICU (N=9073)

SCr Measured (N=885)

SCr Measured (N=1507)

No AKI (N=396) AKI (N=489) No AKI (N=1005) AKI (N=502)
AKI Predictive Models Perform Well in External Validation

ICU

Non-ICU

AUC = 0.74 (0.71–0.78)

AUC = 0.7 (0.67–0.72)
AKI Model Discrimination

ICU

Non-ICU

Predicted Probabilities of AKI

Count
Predicting AKI in REAL TIME

Warning: Acute Kidney Injury Risk
This patient is predicted to have increased risk for acute kidney injury (AKI). Consider assessing renal function.

- Order a BMP for NOW
- Order a BMP for AM
- Decline ordering BMP

Reason for decline: [field]

AKI risk notification is part of a randomized trial; not all patients will receive notifications. More information on the study is available here.

Line Chart

[Graph showing a line chart with multiple lines indicating a trend over time.]
General Conclusions

• Children really are not small adults
  • Application of CDS without consideration of special populations can lead to trouble
  • Also have great opportunities for impact
• Leveraging data already in the health record (genomic or not) provides opportunity for “rapid” intervention
• Electronic health records are a data source and platform for precision medicine for special populations such as children
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