2019 Goldberg Early Investigator Award Lecture

Sara Van Driest, MD, PhD
Assistant Professor of Pediatrics and Medicine
Dr. Goldberg’s Legacy

Peripheral Dopamine Receptors in Cardiovascular Therapy
The Legacy of Leon Goldberg (1927–1989)

Jai D. Kohli, John L. McNay, Sol I. Rajfer, and Michael B. Murphy

Leon Isidore Goldberg, Professor of Pharmacology and Medicine and Chairman of the Committee on Clinical Pharmacology at The University of Chicago, died May 8, 1989, after a brief illness and an illustrious career. In recognition of his outstanding contributions to cardiovascular pharmacology and medicine, Hypertension invited us, Leon’s colleagues during the major part of his career, to review the breadth of innovation he brought to the treatment of cardiovascular disease.

Although we will shortly describe his scientific contributions, it is appropriate to begin with a brief reflection on the personal qualities that endeared Leon to his many colleagues and friends around the world. Among the countless tributes paid after his death, one characteristic was identified above all others: his unassuming, friendly, nonconfrontational approach to life. When, on the losing end of an argument, there was always the graceful exit with “Well, I have only been thinking aloud!”

The circumstances under which one of us (J.D.K.) first met him illustrate the essence of his personality: “It was the unassuming a person Leon was. He was already well-known for his work on dopamine at the time, but he did not react to me not recognizing him, and he later went out of his way to seek me out, a relatively unknown person, to discuss something in which he was genuinely interested.”

There was extraordinary personal generosity to colleagues and staff. Informal visits to his home, any time, on any day, were the norm. Junior faculty and fellows were treated to restaurants, the theater, or even the occasional football game—provided, of course, that they were willing to hear out Leon’s latest theory on dopamine receptors! His willingness to sit on the floor, beer in hand, with student or fellow, casually discussing pharmacology, music, Ulysses, or Finnegans Wake (he was a perennial student of the “Great Books”) made him a much sought after teacher and mentor. His popularity among medical students was also aided by his inability to fail anyone at examination time. There was always some mitigating circumstance, and the erring student would be shamed into the additional necessary study. He started the Clinical

Kohli et al, Hypertension 1991
McDonald et al, J Clin Invest 1964
Using Big Clinical Data for Small (Pediatric) Patients

- Acute Kidney Injury
- Latent Drug Outcomes
- Drug-Gene Interactions
EHRs are a tool for translational research and implementation

Norman Rockwell, *Doctor and Doll*  
*The Saturday Evening Post*, March 29, 1929

“Is Your Doctor Getting Too Much Screen Time?”  
AKI is a problem for pediatric inpatients

Acute Kidney Injury (AKI)

- 1.5-fold or 0.3 mg/dL increase in creatinine
- Increased morbidity, mortality and length of stay
- >5% on wards; >25% in PICU
- Screening can reduce severity

Goldstein et al. Pediatrics 2013
Downes et al. J Cyst Fibros 2014
We can use EHR data to predict AKI risk

EHR Data

Informative?
Independent?
Available in Real-Time?
We can use EHR data to predict AKI risk

\[ X_B = \begin{align*}
33.23485 \\
-0.133488(\text{age of patient in years at time of admission}) \\
+0.0006659806(\text{age} - 0.3225188)^3 \{x_1 \text{ if age} > 0.3225188, x_0 \text{ if not}\} \\
-0.0008929974(\text{age} - 4.298426)^3 \{x_1 \text{ if age} > 4.298426, x_0 \text{ if not}\} \\
+0.0002270168(\text{age} - 15.96222)^3 \{x_1 \text{ if age} > 15.96222, x_0 \text{ if not}\} \\
+0.09773457(\text{number of high risk nephrotoxins}) \\
+0.7827242(\text{number of moderate risk nephrotoxins}) \\
-0.1203862(\text{total number of medications}) \\
-0.003730175(\text{minimum platelet count}) \\
+7.159349 \times 10^{-8}(\text{minimum platelet count} - 109.8)^3 \{x_1 \text{ if plt} > 109.8, x_0 \text{ if not}\} \\
+2.518633 \times 10^{-8}(\text{minimum platelet count} - 278)^3 \{x_1 \text{ if plt} > 278, x_0 \text{ if not}\} \\
+1.802898 \times 10^{-8}(\text{minimum platelet count} - 344.8)^3 \{x_1 \text{ if plt} > 344.8, x_0 \text{ if not}\} \\
+0.2870502(\text{median RDW}) \\
-0.08475973(\text{median RDW} - 12.7)^3 \{x_1 \text{ if RDW} > 12.7, x_0 \text{ if not}\} \\
+0.11691(\text{median RDW} - 13.25)^3 \{x_1 \text{ if RDW} > 13.25, x_0 \text{ if not}\} \\
-0.03215024(\text{median RDW} - 14.7)^3 \{x_1 \text{ if RDW} > 14.7, x_0 \text{ if not}\} \\
-0.6062568(\text{x1 if all Phosphorus below ULN; x0 if not}) \\
+1.045055(\text{x1 if 1 or more Phosphorus above ULN, x0 if not}) \\
-1.660279(\text{x1 if all transaminases below ULN, x0 if not}) \\
-0.5513197(\text{x1 if 1 or more transaminases above ULN; x0 if not}) \\
-4.796936(\text{minimum pH}) \\
+10.15878(\text{minimum pH} - 7.09)^3 \{x_1 \text{ if pH} > 7.09, x_0 \text{ if not}\} \\
-47.40766(\text{minimum pH} - 7.31)^3 \{x_1 \text{ if pH} > 7.31, x_0 \text{ if not}\} \\
+37.24888(\text{minimum pH} - 7.37)^3 \{x_1 \text{ if pH} > 7.37, x_0 \text{ if not}\} \\
+0.2708241(\text{x1 if hypotension, x0 if not})
\end{align*} \]

EHR Implementation
AKI prediction in REAL TIME
Randomized trial of AKI decision support efficacy

VCH Admissions
12/2016-10/2017

ICU

936
Control

973
Intervention

597 (64%)
At Risk

606 (62%)
At Risk

Non-ICU

5505
Control

5492
Intervention

193 (4%)
At Risk

193 (4%)
At Risk

Wang et al. PAS 2018
AKI risk alerts work, sometimes...

**ICU**

- Control (N=597): 59%
- Intervention (N=606): 68%

\[ p = 0.001 \]

**Non-ICU**

- Control (N=193): 45%
- Intervention (N=193): 39%

\[ p = 0.17 \]

Wang et al. PAS 2018
What are other AKI risk factors?

- Increased AKI reported in adults treated with piperacillin/tazobactam (TZP) and vancomycin
- Studies difficult to interpret due to confounding by indication
Vancomycin + piperacillin/tazobactam is more nephrotoxic than vancomycin + cefepime.

**Univariate Analysis of AKI in 228 Matched Children**

<table>
<thead>
<tr>
<th>AKI Incidence</th>
<th>Vancomycin + Cefepime (N=114)</th>
<th>Vancomycin + TZP (N=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>8%</td>
<td>29%</td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p*<0.001

**Adjusted Analysis of AKI in 228 Matched Children**

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin + Cefepime Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin + TZP</td>
<td>2.5 [1.1-5.8]</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, nephrotoxins, and vancomycin dose

Cook et al. *JPIDS* 2018
Can we protect against AKI?

- Half of pediatric cardiac surgery patients have post-op AKI
- Many factors...

Van Driest et al. JAMA Peds 2018
### AKI and Acetaminophen in 666 Pediatric Cardiac Surgery Patients

<table>
<thead>
<tr>
<th></th>
<th>No AKI (N=325)</th>
<th>AKI (N=341)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Acetaminophen Given</td>
<td>305 (94%)</td>
<td>289 (85%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acetaminophen dose (mg/kg)</td>
<td>78 (43-104)</td>
<td>47 (18-88)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Van Driest et al. JAMA Peds 2018
Association holds with adjustment

OR = 0.86 (0.82-0.90)
Association holds with adjustment and in replication cohort

Van Driest et al. JAMA Peds 2018
Changing trajectories of health

Exposure

Organ Function

Age (years)

Normal Function
Sub-clinical Dysfunction
Clinical Disease
Using Big Clinical Data for Small (Pediatric) Patients

- Acute Kidney Injury
- Latent Drug Outcomes
- Drug-Gene Interactions
GWAS and PheWAS

Phenotype → Genome

Genome Wide Association

Genotype → Phenome

Phenome Wide Association

Denny et al. Nat Biotechnol 2013
PheWAS can be used for more than genetics

- A drug exposure
- A laboratory test result
- A disease
- A single SNP
- A genetic pathway or risk score
- Measured or "imputed" gene expression

The curated EHR-based phenome

Associated phenotypes
PheWAS may help us uncover new drug effects

Choi et al. Bioinformatics 2018
### Proof-of-principle in a medical home cohort

<table>
<thead>
<tr>
<th>Group</th>
<th>All</th>
<th>Gentamicin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Exposed</td>
</tr>
<tr>
<td><strong>Exposure Status</strong></td>
<td>11,116</td>
<td>1,202</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Female (%)</td>
<td>5,412</td>
<td>521</td>
</tr>
<tr>
<td>(48.7%)</td>
<td>(43.3%)</td>
<td>(49.4%)</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>10.9</td>
<td>8.7</td>
</tr>
<tr>
<td>(4.6)</td>
<td>(3.7)</td>
<td>(4.6)</td>
</tr>
<tr>
<td>N White (%)</td>
<td>4,061</td>
<td>411</td>
</tr>
<tr>
<td>(36.5%)</td>
<td>(34.2%)</td>
<td>(36.9%)</td>
</tr>
</tbody>
</table>

Choi et al. *Bioinformatics* 2018
Unadjusted PheWAS results indicate a multitude of associations to gentamicin exposure.
PheWAS on drug exposures require updated methods

“Standard”
• Adjust by demographics
• Logistic regression using maximum likelihood (Wald)

Supported by Simulation
• Adjust by propensity score
  – Beats demographic adjustment
  – Beats propensity score matching
• Logistic regression using penalized maximum likelihood (aka Firth’s)
  – Handles complete separation
  – Reduces bias

Choi et al. *Bioinformatics* 2018
Adjusted PheWAS results indicate interesting associations to early gentamicin exposure.
New results validate the PheRS approach

A Nationwide Study in Denmark of the Association Between Treated Infections and Disorders in Children

Kohler-Forsberg et al. JAMA Psychiatry 2018
Using Big Clinical Data for Small (Pediatric) Patients

- Acute Kidney Injury
- Latent Drug Outcomes
- Drug-Gene Interactions
Genes influence drug response through drug metabolism (and other ways)
Thiopurine metabolism depends on TPMT & NUDT15

Gianluigi et al, Pharmacogenet Genomics 2010
Pharmacogenomic (PGx) Resource For Enhanced Decisions In Care & Treatment

Current Platform

**TPMT** – Thiopurine Drugs

**CYP3A5** – Tacrolimus

**CYP2D6** – Codeine, Tramadol

**CYP2C19** – Clopidogrel, Voriconazole

**CYP2C9, VKORC1, CYP4F2** – Warfarin

**SLCO1B1** – Simvastatin
Actionable pharmaco-genotypes are common

Van Driest et al, *Clin Pharm Ther* 2014
Actionable pharmaco-genotypes are common

Van Driest et al, Clin Pharm Ther 2014
Few pediatric patients undergo PGx testing
Pediatric Exposures to “PGx drugs”

41 Drugs with known PGx

De-identified EHR: 10 years of pediatric exposures

Annual Pediatric Drug Exposures

- > 500: 10
- 100-500: 13
- 50-100: 3
- 10-50: 5
- < 10: 10

Which PGx associations have pediatric evidence?

Why aren’t we doing PGx testing for risperidone?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Variant(s) Assayed</th>
<th>Population</th>
<th>n</th>
<th>Significant Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>CYP2D6</td>
<td><em>3~</em>7, duplication</td>
<td>5-17-year-olds with pervasive developmental disorder</td>
<td>25</td>
<td>Yes</td>
</tr>
<tr>
<td>Risperidone</td>
<td>CYP2D6</td>
<td><em>3~</em>5, duplication</td>
<td>4-15-year-olds treated with risperidone for psychiatric or neurodevelopmental conditions</td>
<td>19</td>
<td>No</td>
</tr>
<tr>
<td>Risperidone</td>
<td>CYP2D6</td>
<td><em>3~</em>6, duplication</td>
<td>3-21-year-olds with ASD</td>
<td>45</td>
<td>Yes</td>
</tr>
<tr>
<td>Risperidone</td>
<td>CYP2D6</td>
<td>*4</td>
<td>9~20-year-olds with schizophrenia or bipolar disorder</td>
<td>81</td>
<td>Yes</td>
</tr>
<tr>
<td>Risperidone</td>
<td>CYP2D6</td>
<td>*10</td>
<td>8~20-year-olds treated with risperidone for mental or behavioral disorder</td>
<td>120</td>
<td>No</td>
</tr>
<tr>
<td>Risperidone</td>
<td>CYP2D6</td>
<td>*4, *5, *10, *41</td>
<td>3~19-year-olds with ASD</td>
<td>147</td>
<td>No</td>
</tr>
<tr>
<td>Risperidone</td>
<td>CYP2D6</td>
<td>*10</td>
<td>8~20-year-olds treated with risperidone for mental and behavioral disorders</td>
<td>120</td>
<td>Yes</td>
</tr>
<tr>
<td>Risperidone</td>
<td>CYP2D6</td>
<td><em>3~</em>6, *9, *10, *41, duplication</td>
<td>9~93-year-olds with risperidone TDM</td>
<td>425</td>
<td>Yes</td>
</tr>
<tr>
<td>Risperidone</td>
<td>CYP2D6</td>
<td>Affymetrix DMET Plus GeneChip microarray</td>
<td>Children with ASD (median age 8.8 (IQR 3.4-18.6) years)</td>
<td>102</td>
<td>Yes</td>
</tr>
<tr>
<td>Risperidone</td>
<td>CYP2D6</td>
<td>*4, *5, *10, *41</td>
<td>Children with ASD (median age 10 (IQR 7~12.15) years)</td>
<td>97</td>
<td>Yes</td>
</tr>
</tbody>
</table>
The BioVU resource links EHR data to DNA

Electronic Health Records Data
- Notes
- Lab Results
- Drug Exposure
- Billing Codes

De-Identification

DNA from Discarded Blood Samples

Synthetic Derivative
~3 million individuals

BioVU
>240,000 DNA samples
>30,000 pediatric
CYP2D6 status is associated with risperidone adverse events

### Cohort Summary Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=257</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>8.3 (6.3-10.5)</td>
</tr>
<tr>
<td>Male Sex</td>
<td>188 (73%)</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>76 (30%)</td>
</tr>
</tbody>
</table>

#### Metabolizer Status

- Ultrarapid: 6 (2%)
- Normal: 218 (85%)
- Intermediate: 18 (7%)
- Poor: 15 (6%)

Number (%) or Median (Interquartile Range)

### Univariate Analysis of Adverse Drug Events in 251 Children

- **Poor or Intermediate** (n=33): 45 Adverse Drug Event Rate
- **Normal** (n=218): 27 Adverse Drug Event Rate

**p=0.04**

Neely et al. PIII-092

Oshikoya et al. *Pediatric Res* 2019
Proton Pump Inhibitor PGx

Ward & Kearns. Pediatric Drugs 2013
Lima et al. J Pediatrics 2013
CYP2C19 status is associated with PPI adverse events

Cohort Summary Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=670</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Months)</td>
<td>7 (3-13)</td>
</tr>
<tr>
<td>Male Sex</td>
<td>378 (56%)</td>
</tr>
<tr>
<td>Annual Infection Events (per person)</td>
<td>2.1</td>
</tr>
<tr>
<td>Metabolizer Status</td>
<td></td>
</tr>
<tr>
<td>Rapid/Ultrarapid</td>
<td>220 (33%)</td>
</tr>
<tr>
<td>Normal</td>
<td>267 (40%)</td>
</tr>
<tr>
<td>Intermediate/Poor</td>
<td>183 (27%)</td>
</tr>
</tbody>
</table>

Number (%) or Median (Interquartile Range)

Univariate Analysis of Infection Events in 670 Children

- Normal (n=267) Annual Infection Event Rate: 2.4
- Rapid/Ultrarapid (n=220) Annual Infection Event Rate: 1.8

p=0.03

Bernal et al. PAS 2018
We continue to build evidence for pediatric PGx

![Number of Manuscripts](image)

Making progress in pediatric PGx

Impact of SLCO1B1 Genotype on Pediatric Simvastatin Acid Pharmacokinetics

Jonathan B. Wagner, Haandel, PhD2,3, An Geetha Raghuveer, and J. Steven Leed

A Population-Based Pharmacokinetic Model Approach to Pantoprazole Dosing for Obese Children and Adolescents

Valentina Shakhnovich, Chad E. Livingston2

Influence of CYP2C19 Metabolizer Status on Escitalopram/Citalopram Tolerability and Response in Youth With Anxiety and Depressive Disorders

Stacey L. Aldrich1,2, Ethan A. Powel1, Cynthia A. Prows2,4, Lisa J. Martin1,2, Jeffrey R. Straw1,6 and Laura B. Ramsey1,3*

CYP2D6 pharmacogenetic and oxycodone pharmacokinetic association study in all patients

Rajiv Balyan1,2, Marc Mecoli1,3, Raja Venkatasubramanian1,2, Vidya Chidambaram1,3, Nichole Kamos3, Smokey Clay1,3, David L Moore4,3, Jagroop Mavi1,3, Chris D

Optimization of Intestinal and Hepatic CYP3A-Mediated clearance of Midazolam in Children Using a Physiological Pharmacokinetic Modelling Approach

1• Huxin Yu1,2, Elke H. J. Krehel1, Semra Palić1,3, Margreke J. E. Brill4, Jeffrey S. Barrett5,6, 5,7,8, Saskia N. de Wildt9,10, Catherine A. J. Knibbe1,11

Aldrich, et al. Front Pharmacol 2019
Complex genomic methods needed to study novel associations to complex phenotypes
Hope for the future...

I am choosing the safest drug for you, based on your history and your genome...

Acknowledgements

AKI Risk Prediction
• Tracy McGregor
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• Jonathan Mosley

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