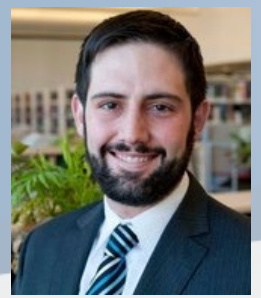
VANDERBILT UNIVERSITY

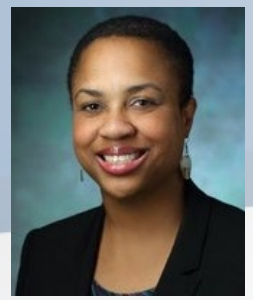
2019 Goldberg Early Investigator Award Lecture

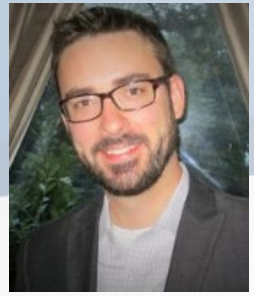
Sara Van Driest, MD, PhD

Assistant Professor of Pediatrics and Medicine

Monroe Carell Jr. Children's Hospital at Vanderbilt


David Strauss

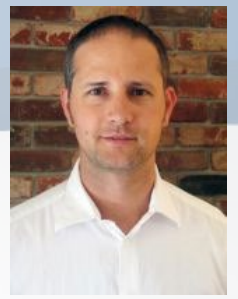

Namandje Bumpus

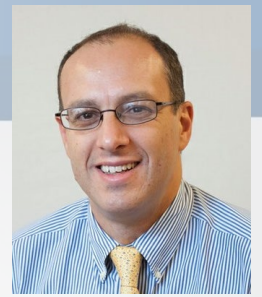

Michael Pacanowski


Minoli Perera


Liewei Wang


Mikko Niemi


Nadav Ahituv


Federico Innocenti


Michael Maitland

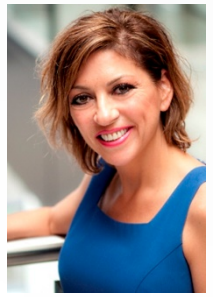

Susan Abdel-Rahman


Julia Kirchheiner


Angela Kashuba


Sean Hennessy


Sebastian Schneeweiss


Micheline Piquette-Miller

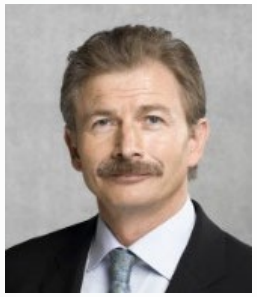

William Figg

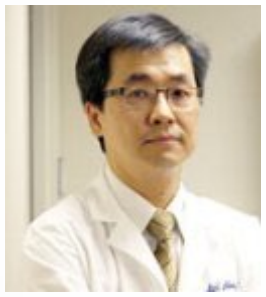

Jaap Mandema


Julie Johnson


Rachel Tyndale


Deanna Kroetz

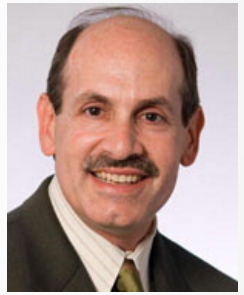

Gerd Geisslinger


Richard Kim


Andre Terzic


Mary Relling

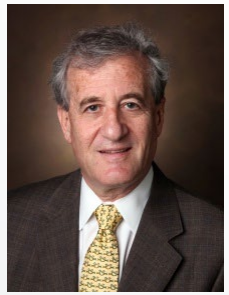

Michael Rieder


Jerry Gurwitz


Stephen Hall


Charles Flexner


Lawrence Miller


Dan Roden


Bill Evans


Kathy Giacomini


Brian Hoffman


Donald Stanski


Oscar Laskin


Eric Brass

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 Isodore 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!"

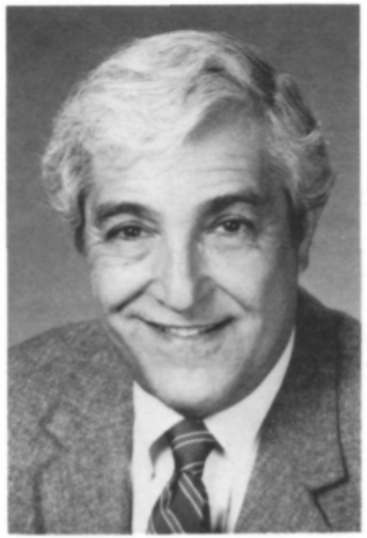


FIGURE 1. *Leon Goldberg.*

The circumstances under which one of us (J.D.K.) first met him illustrates 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 my 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

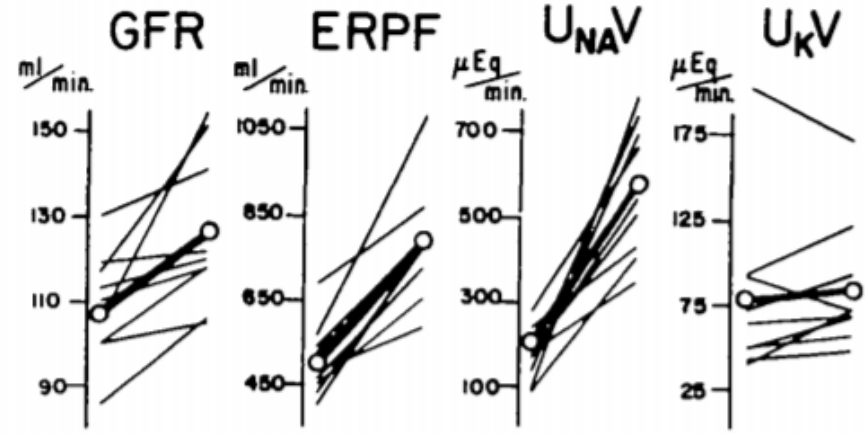
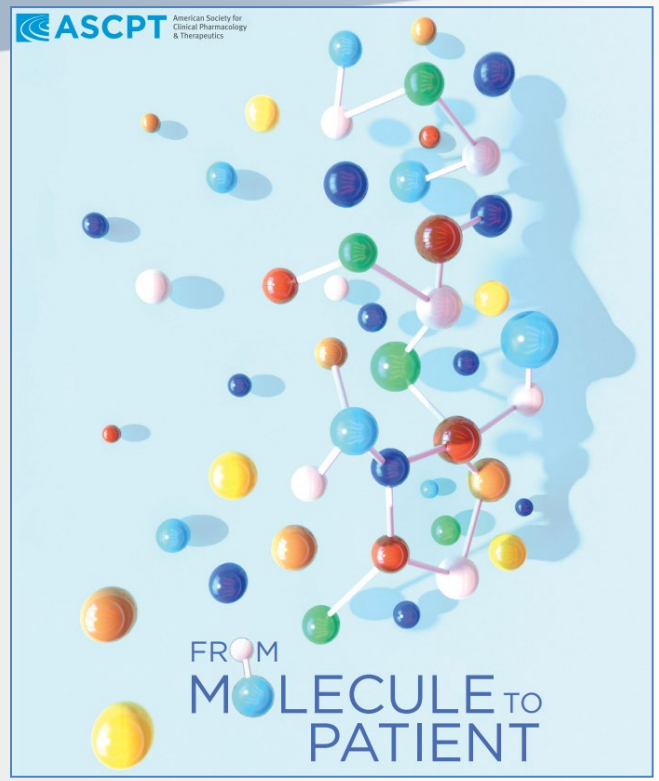
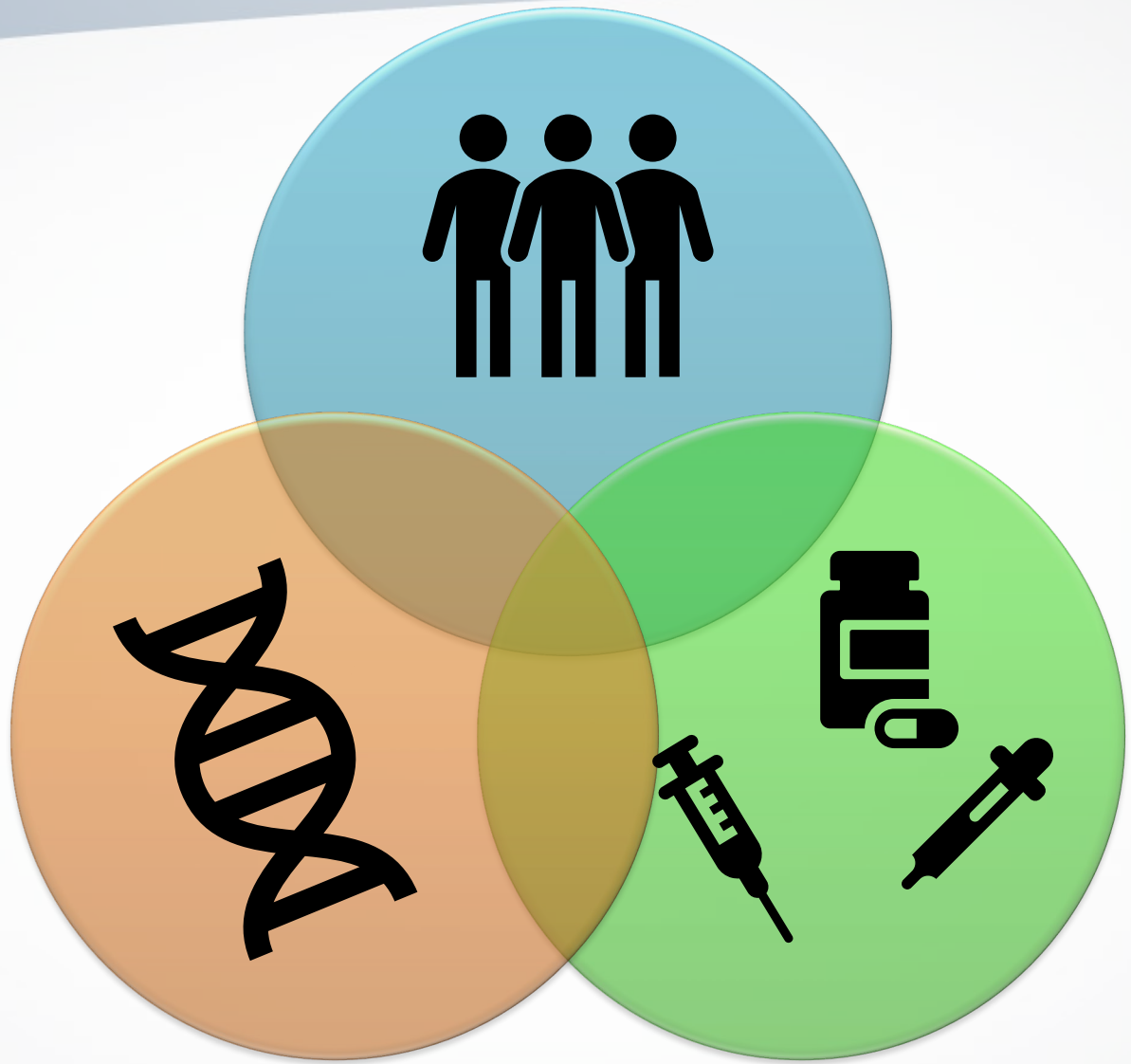


FIGURE 3. *Plots showing effects of intravenous dopamine on glomerular filtration rate (GFR), estimated renal plasma flow (ERPF), sodium excretion (UN_aV), and potassium excretion (U_RV) in normal subjects.*

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?"
The Wall Street Journal, December 14, 2015

AKI is a problem for pediatric inpatients

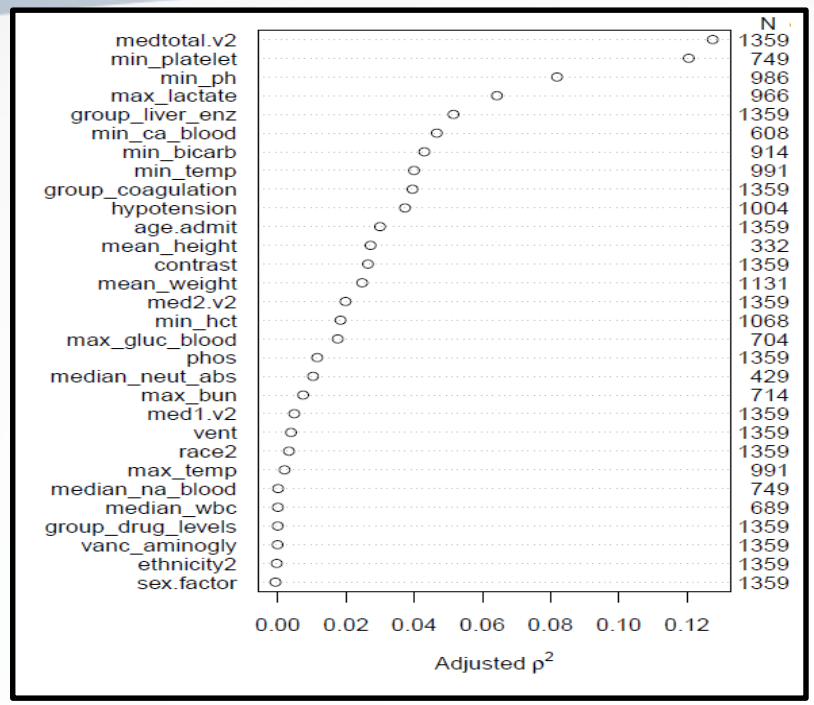
Acute Kidney Injury (AKI)

- 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**

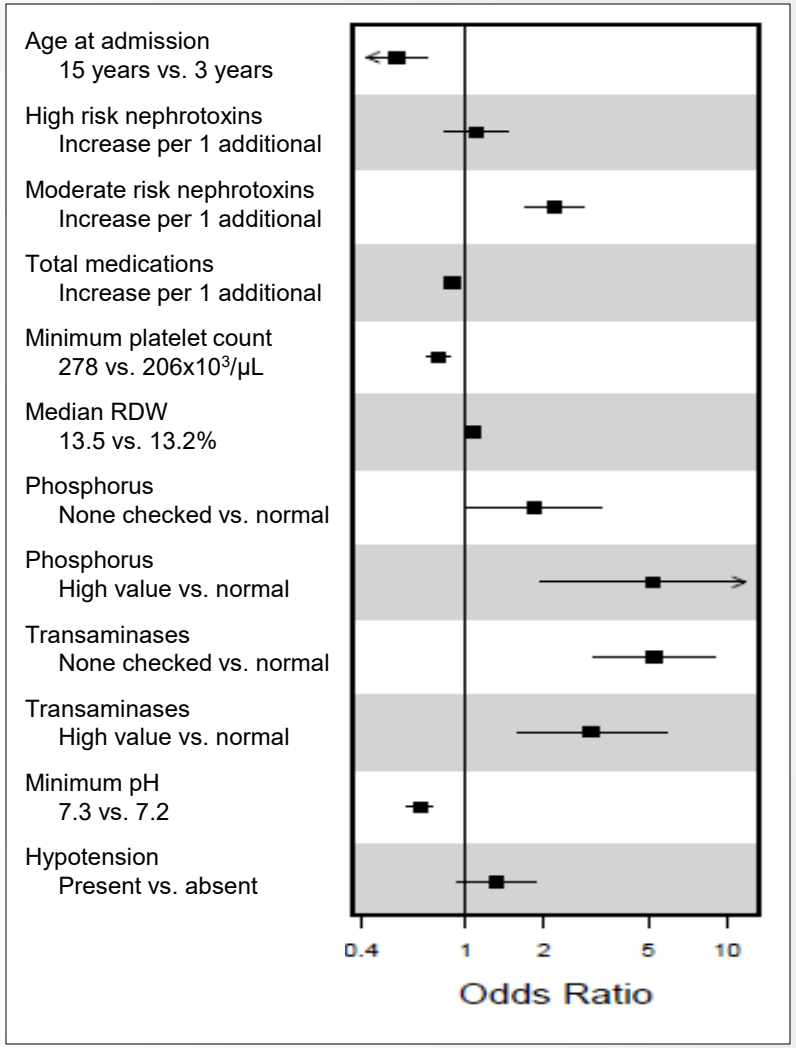
McGregor et al, *Am J Kidney Dis* 2016
Goldstein et al. *Pediatrics* 2013
Downes et al. *J Cyst Fibros* 2014

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

$X\beta =$
33.23465
− 0.133488(age of patient in years at time of admission)
+ 0.0006659806(age − 0.3225188)^3 {x1 if age>0.3225188, x0 if not}
− 0.0008929974(age − 4.298426)^3 {x1 if age>4.298426, x0 if not}
+ 0.0002270168(age − 15.96222)^3 {x1 if age>15.96222, x0 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)
+ 7.159349×10^{-9}(minimum platelet count − 109.8)^3 {x1 if plt>109.8, x0 if not}
− 2.518633×10^{-8}(minimum platelet count − 278)^3 {x1 if plt>278, x0 if not}
+ 1.802698×10^{-8}(minimum platelet count − 344.8)^3 {x1 if plt>344.8, x0 if not}

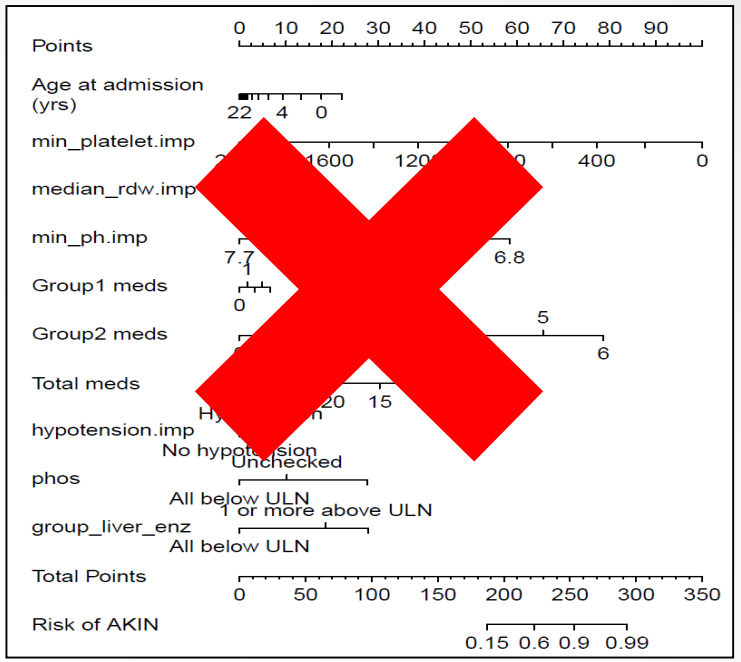
+ 0.2870502(median RDW)
− 0.08475973(median RDW − 12.7)^3 {x1 if RDW>12.7, x0 if not}
+ 0.11691(median RDW − 13.25)^3 {x1 if RDW>13.25, x0 if not}
− 0.03215024(median RDW − 14.7)^3 {x1 if RDW>14.7, x0 if not}

− 0.6062568{x1 if all Phosphorus below ULN; x0 if not}
+ 1.045055{x1 if 1 or more Phosphorus above ULN, x0 if not}

− 1.660279{x1 if all transaminases below ULN, x0 if not}
− 0.5513197{x1 if 1 or more transaminases above ULN; x0 if not}

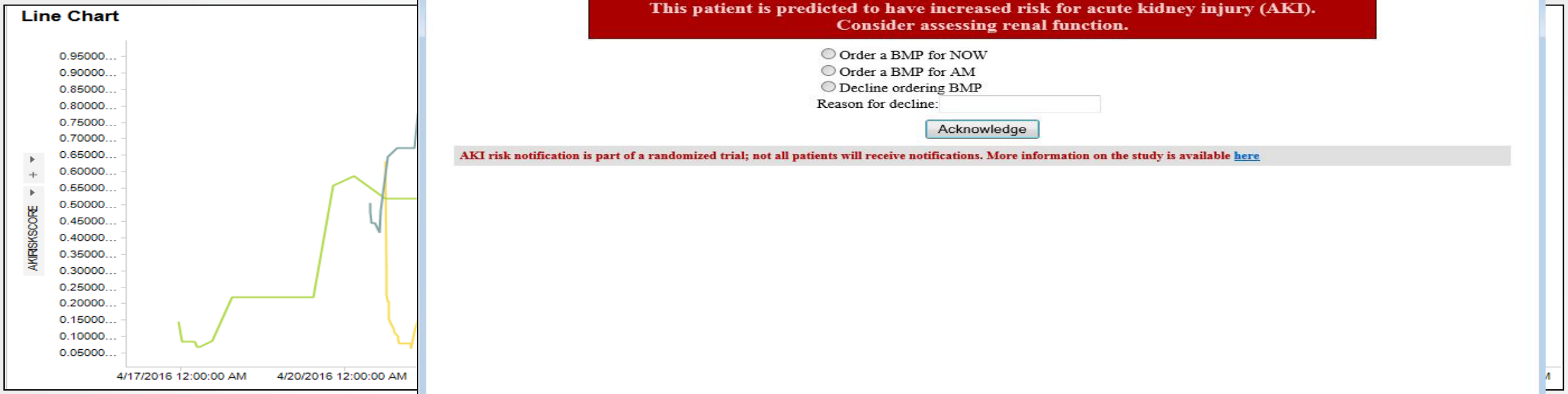
− 4.796936(minimum pH)
+ 10.15878(minimum pH − 7.09)^3 {x1 if pH>7.09, x0 if not}
− 47.40766(minimum pH − 7.31)^3 {x1 if pH>7.31, x0 if not}
+ 37.24888(minimum pH − 7.37)^3 {x1 if pH>7.37, x0 if not}

+ 0.2708241{x1 if hypotension, x0 if not}



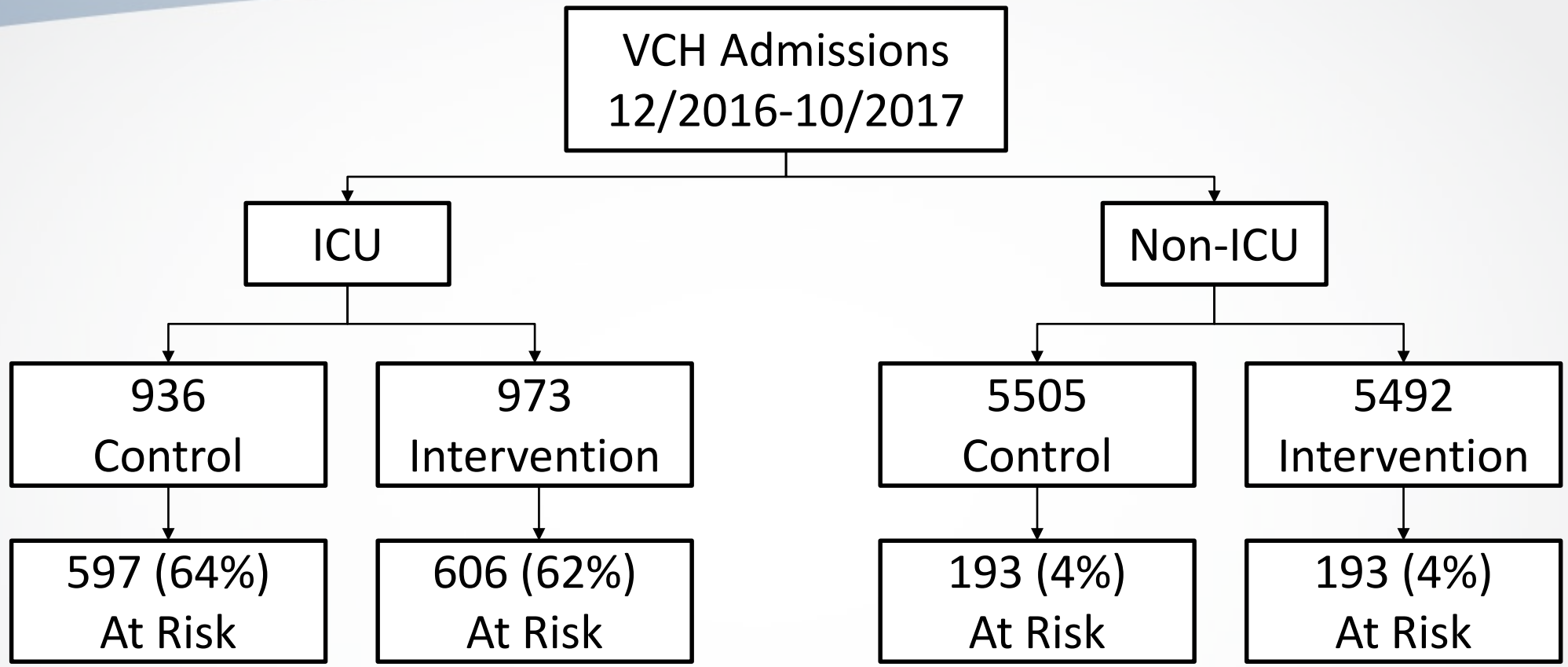
EHR Implementation

AKI prediction in REAL TIME



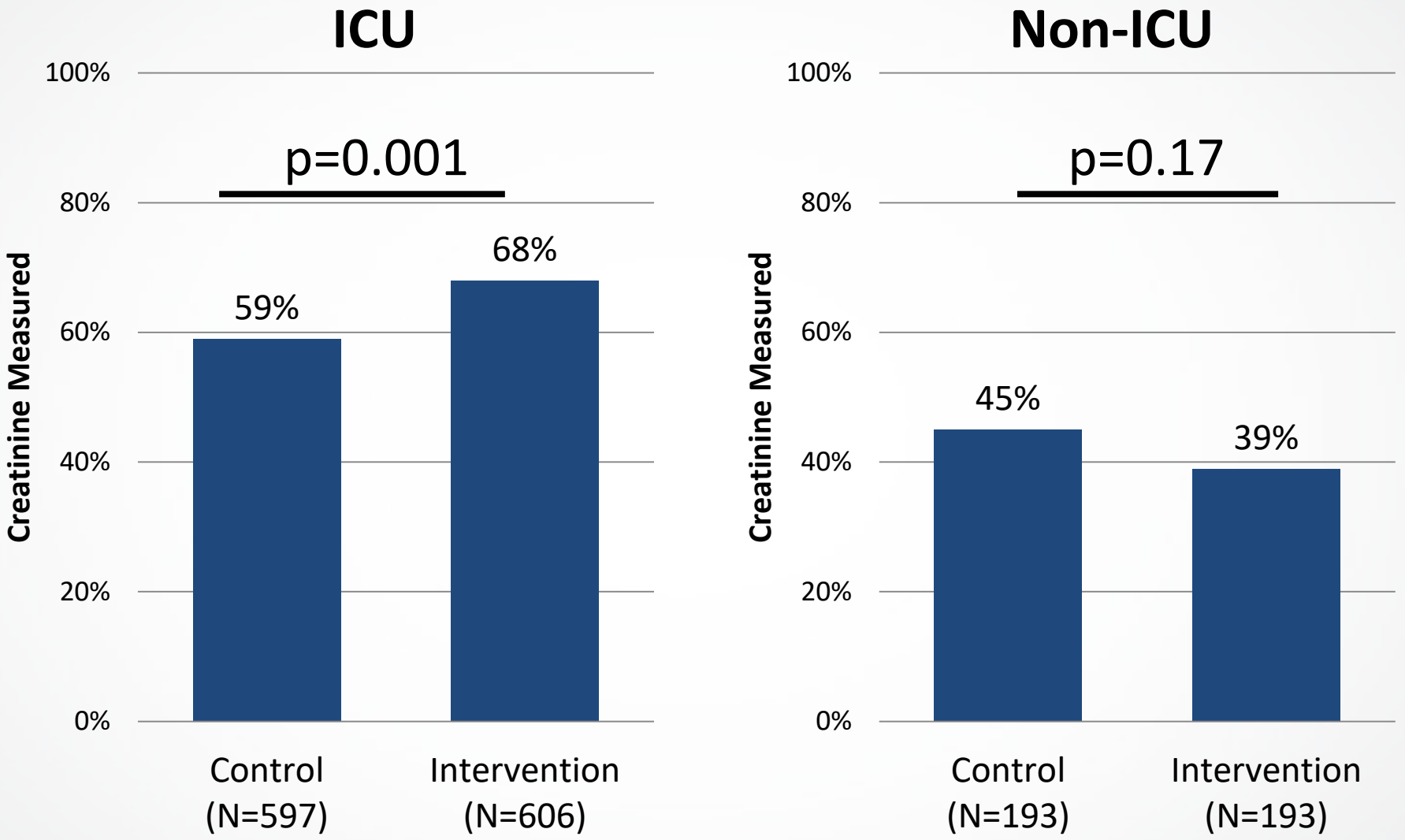
Wang et al. PAS 2018

Randomized trial of AKI decision support efficacy



Wang et al. PAS 2018

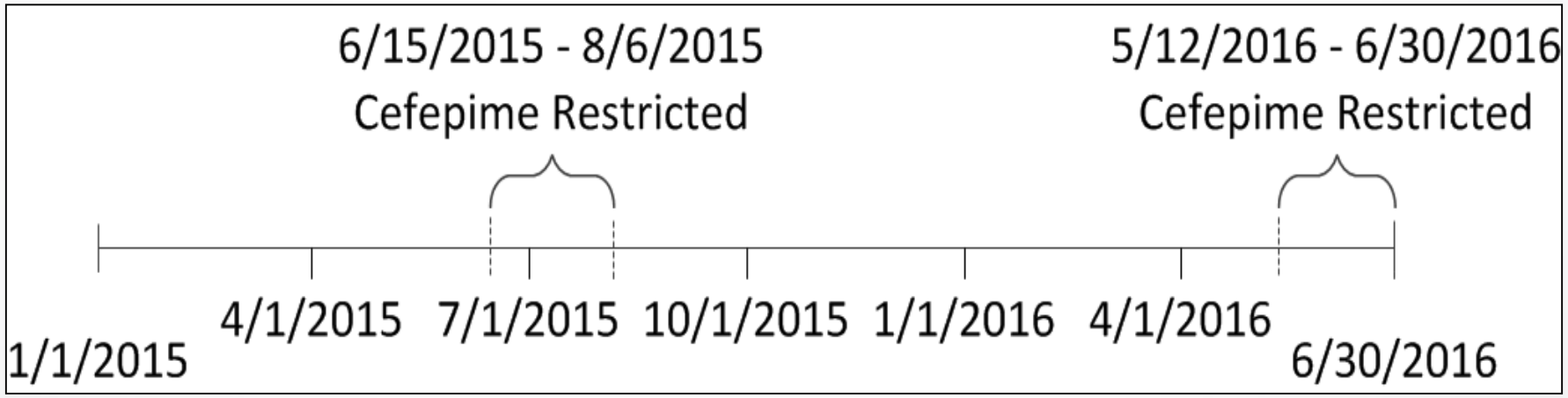
AKI risk alerts work, sometimes…



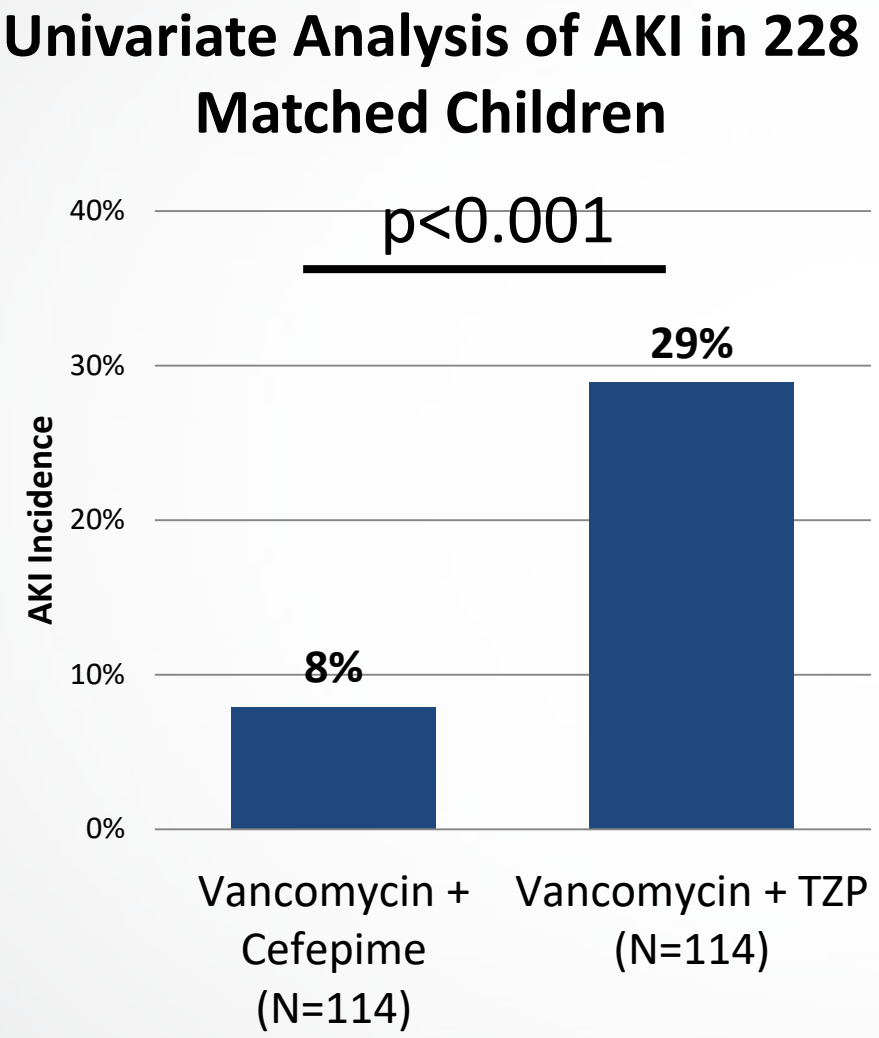
Wang et al. PAS 2018

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



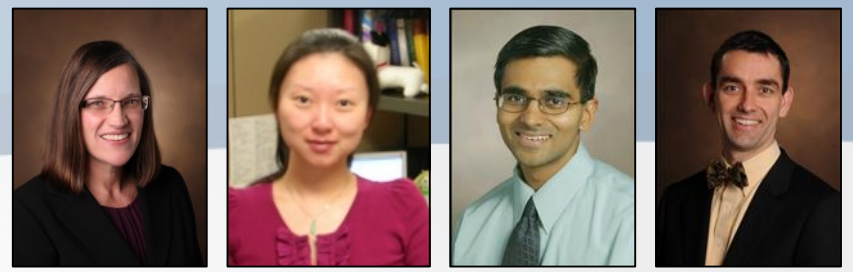
Vancomycin + piperacillin/tazobactam is more nephrotoxic than vancomycin + cefepime



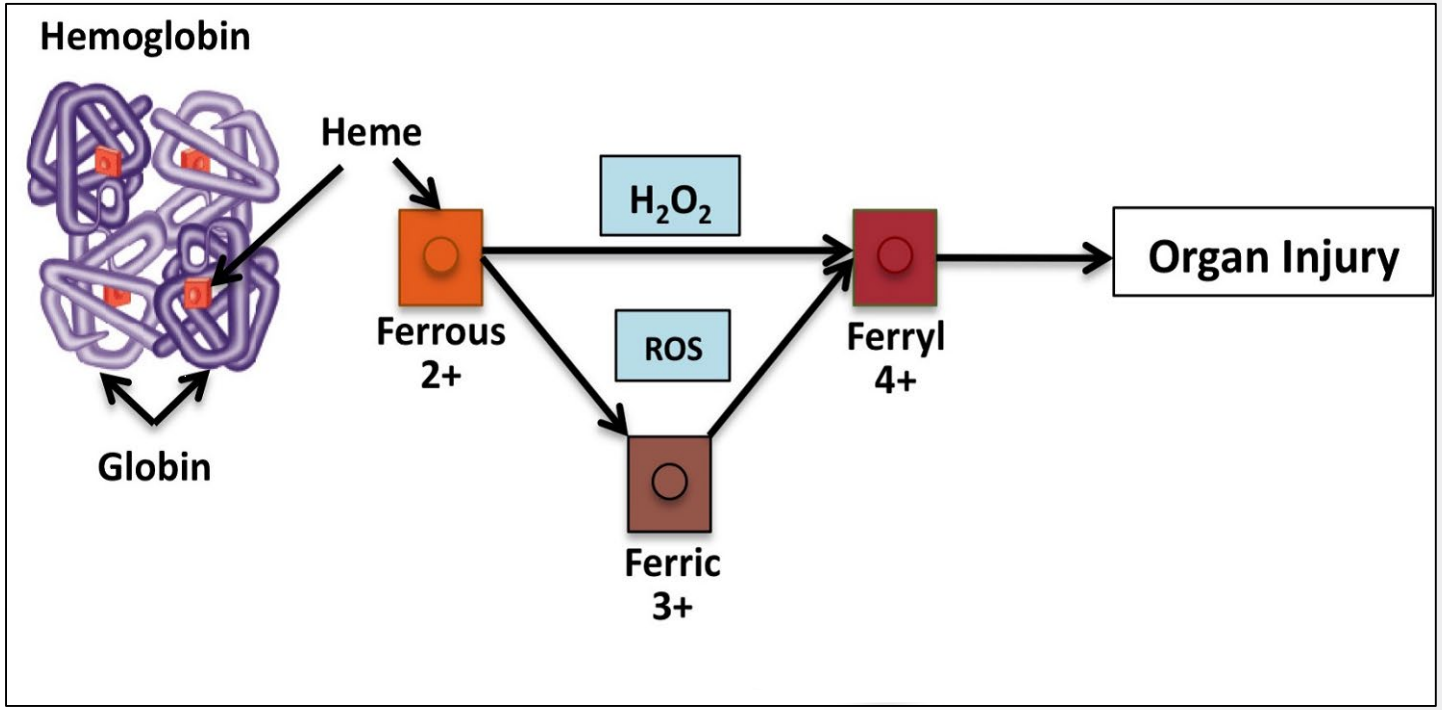
Adjusted Analysis of AKI in 228 Matched Children		
	Odds Ratio [95% CI]	**p-value**
Vancomycin + Cefepime	Reference	
Vancomycin + TZP	2.5 [1.1-5.8]	0.03
Adjusted for age, sex, nephrotoxins, and vancomycin dose		

Cook et al. *JPIDS* 2018

Can we protect against AKI?



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



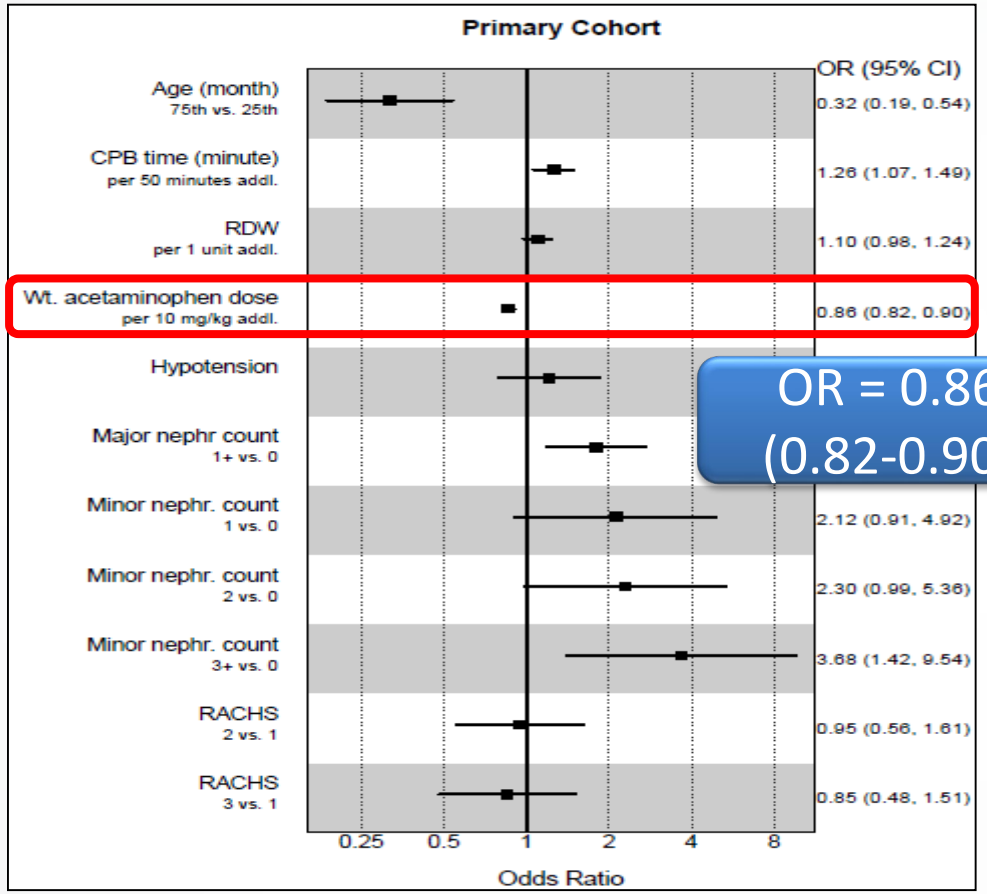
Van Driest et al. *JAMA Peds* 2018

Acetaminophen associated with less AKI

AKI and Acetaminophen in 666 Pediatric Cardiac Surgery Patients			
	No AKI (N=325)	**AKI (N=341)**	**P-value**
Any Acetaminophen Given	305 (94%)	289 (85%)	<0.001
Acetaminophen dose (mg/kg)	78 (43-104)	47 (18-88)	<0.001

Van Driest et al. *JAMA Peds* 2018

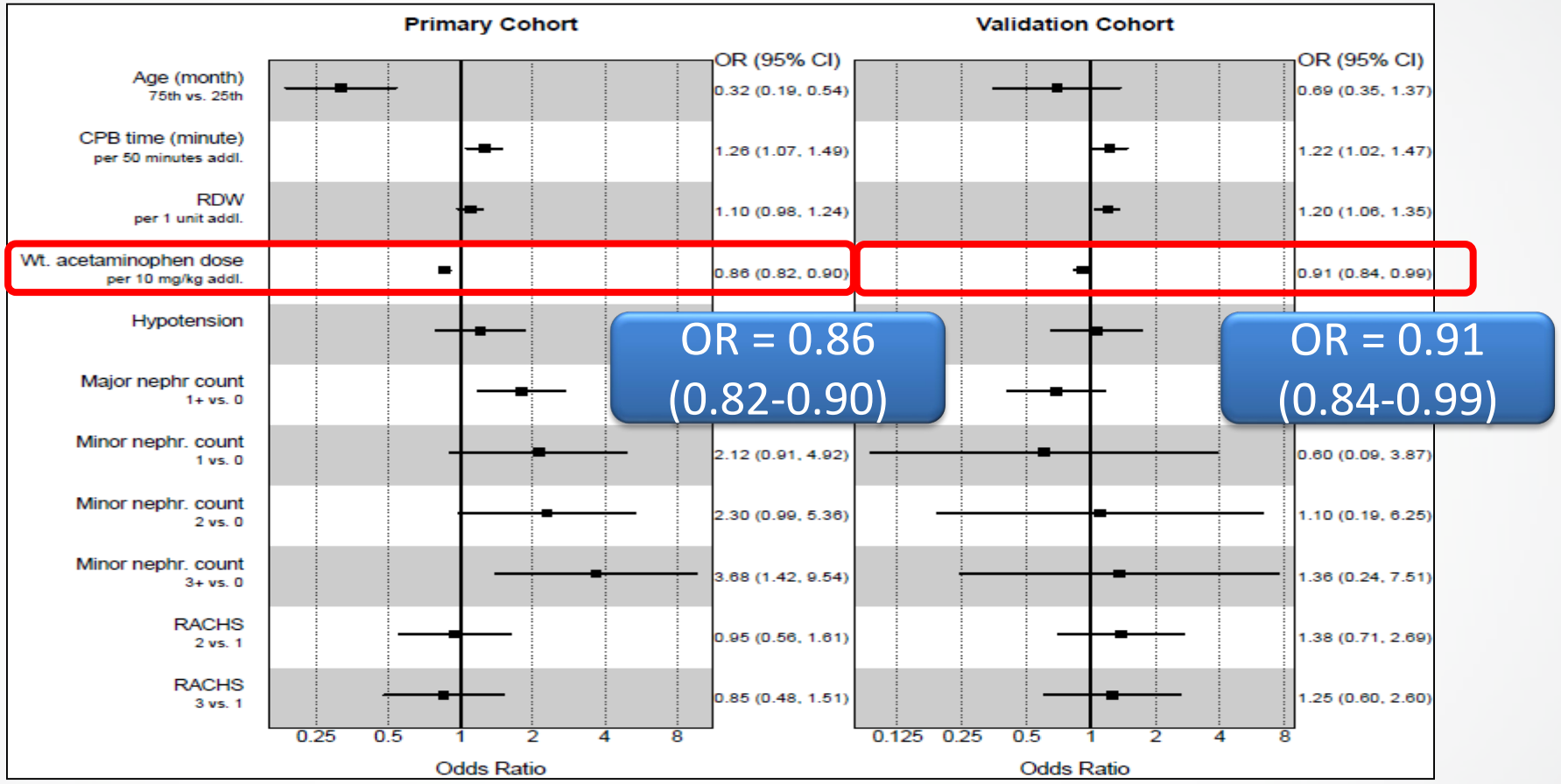
Association holds with adjustment



OR = 0.86 (0.82-0.90)

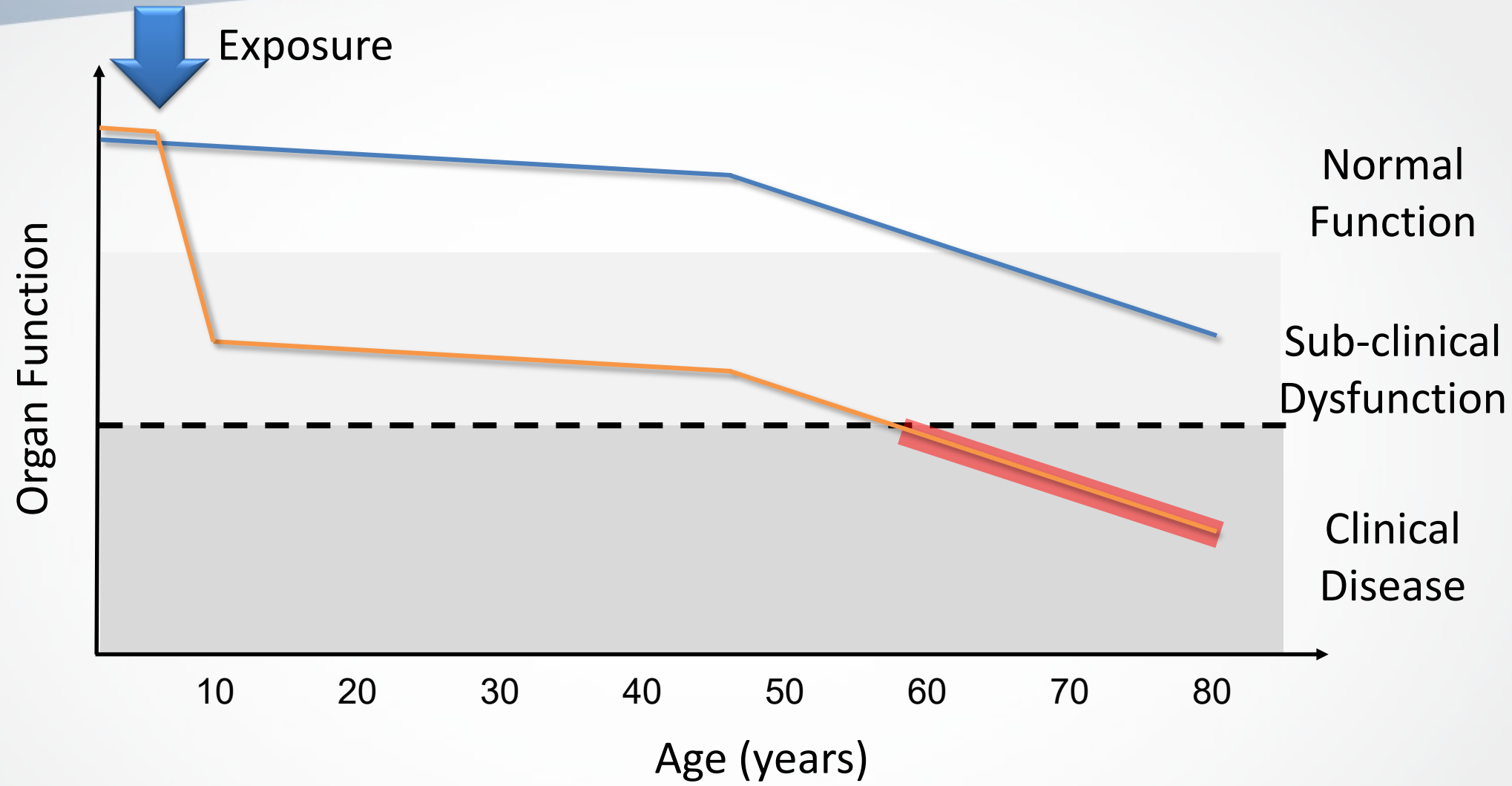
Van Driest et al. *JAMA Peds* 2018

Association holds with adjustment and in replication cohort

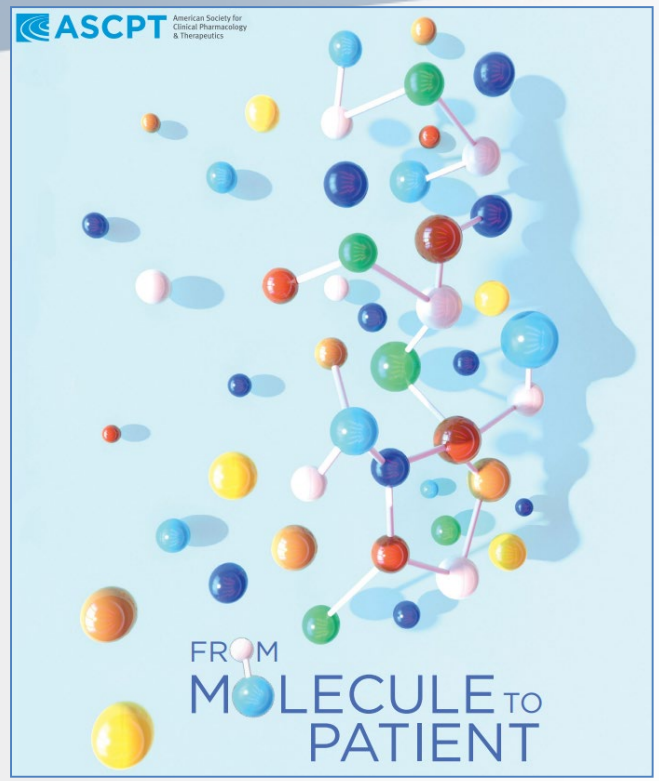



Van Driest et al. *JAMA Peds* 2018

Changing trajectories of health

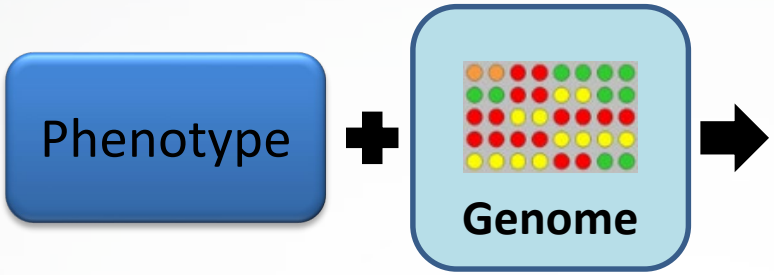


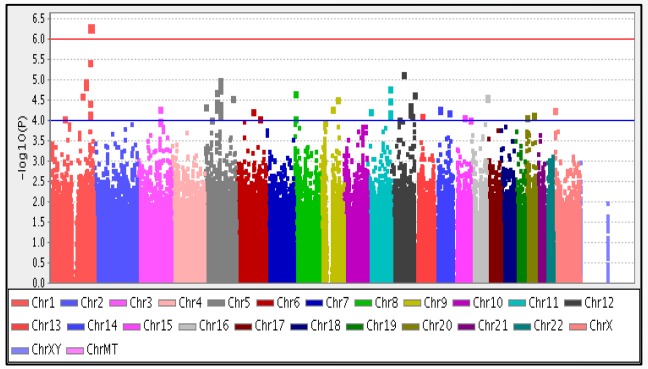
Using Big Clinical Data for Small (Pediatric) Patients



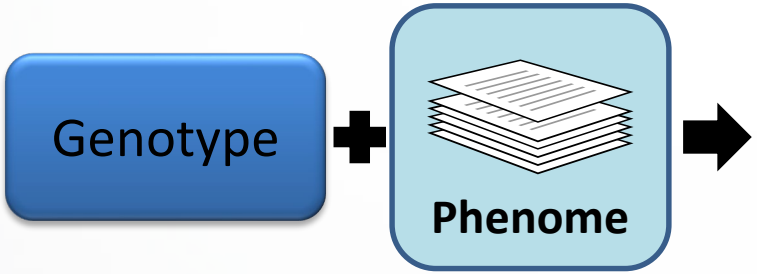
- Acute Kidney Injury
- Latent Drug Outcomes
- Drug-Gene Interactions

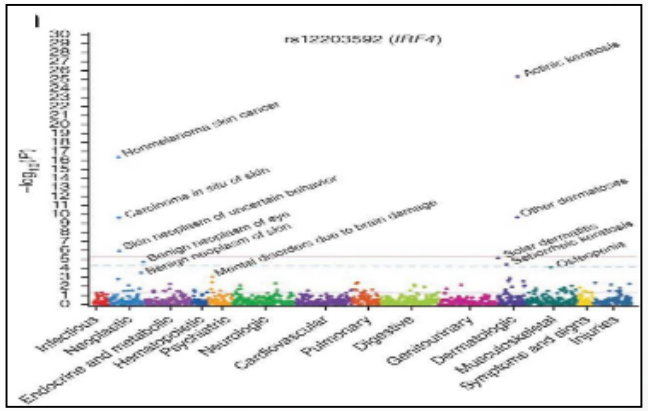
GWAS and PheWAS





Genome Wide Association

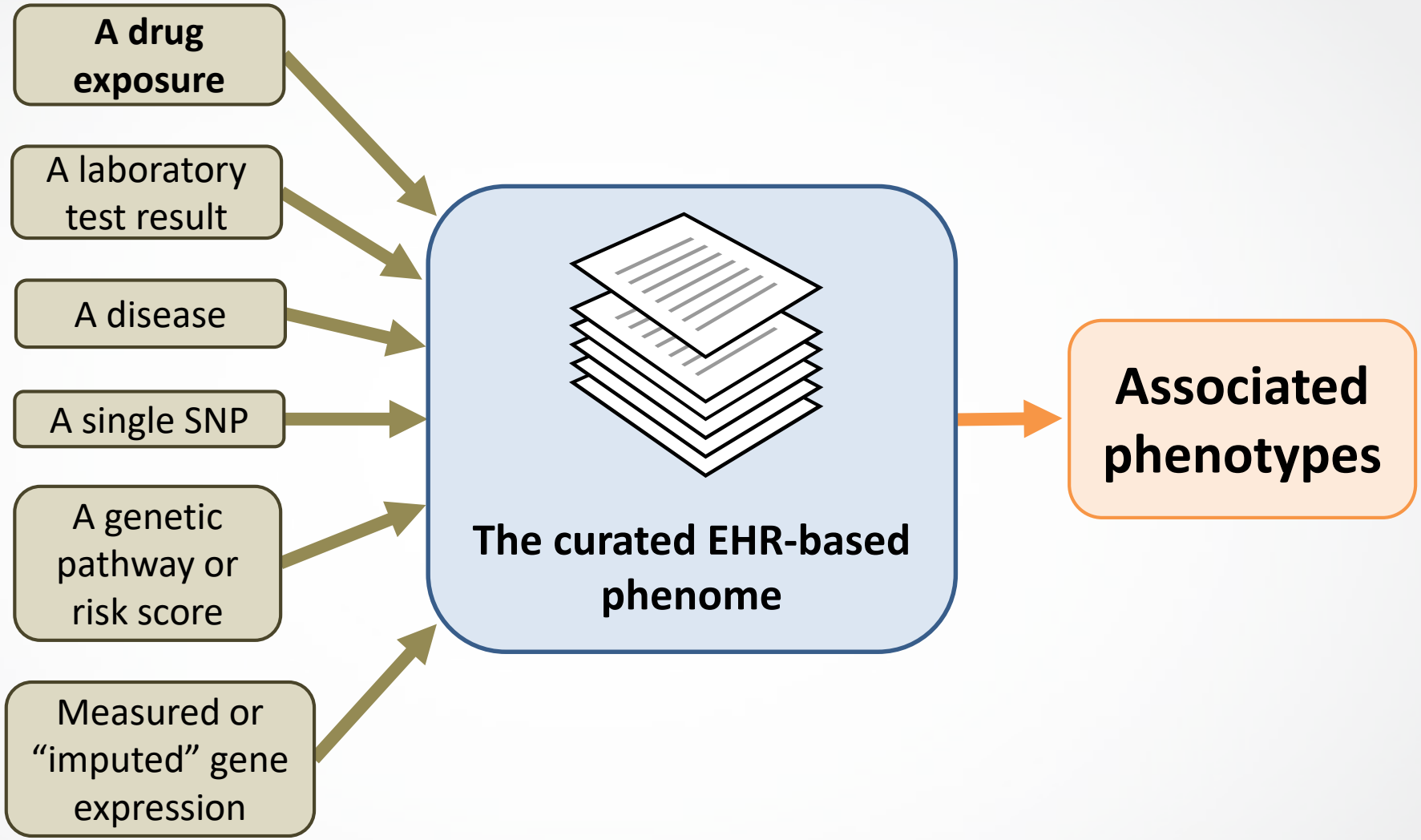




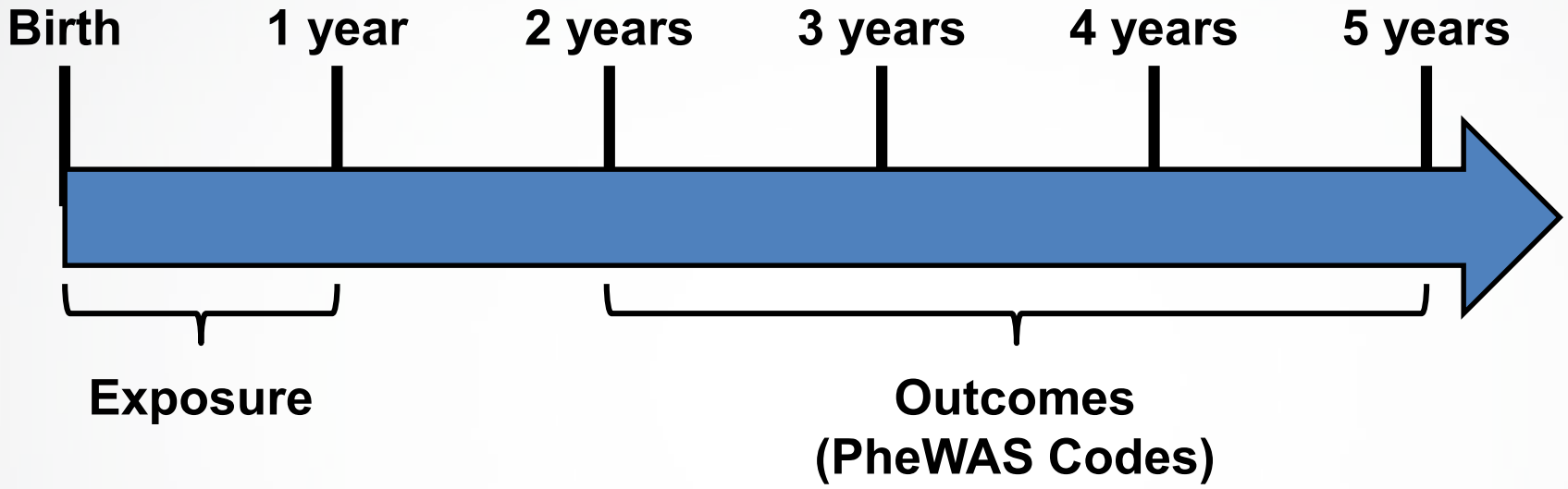
Phenome Wide Association

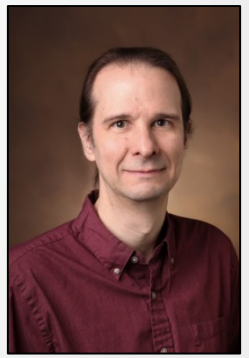
Denny et al. *Nat Biotechnol* 2013

PheWAS can be used for more than genetics



PheWAS may help us uncover new drug effects





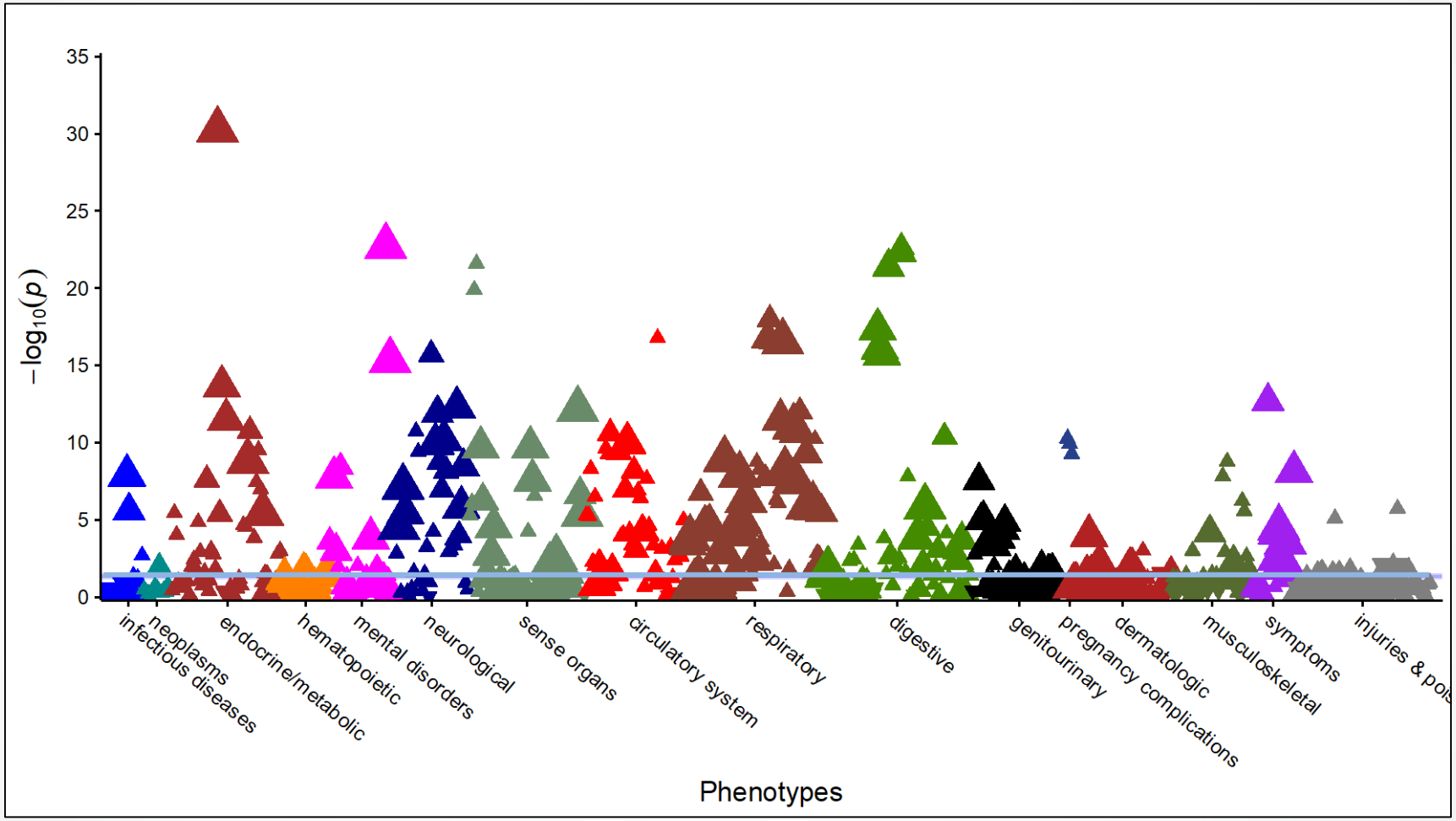
Choi et al. *Bioinformatics* 2018

Proof-of-principle in a medical home cohort

Group	All	Gentamicin	
Exposure Status	All	Exposed	Unexposed
N	11,116	1,202	9,589
N Female (%)	5,412 (48.7%)	521 (43.3%)	4,736 (49.4%)
Age (SD)	10.9 (4.6)	8.7 (3.7)	11.1 (4.6)
N White (%)	4,061 (36.5%)	411 (34.2%)	3,542 (36.9%)

Choi et al. *Bioinformatics* 2018

Unadjusted PheWAS results indicate a multitude of associations to gentamicin exposure



Choi et al. *Bioinformatics* 2018

PheWAS on drug exposures require updated methods

"Standard"

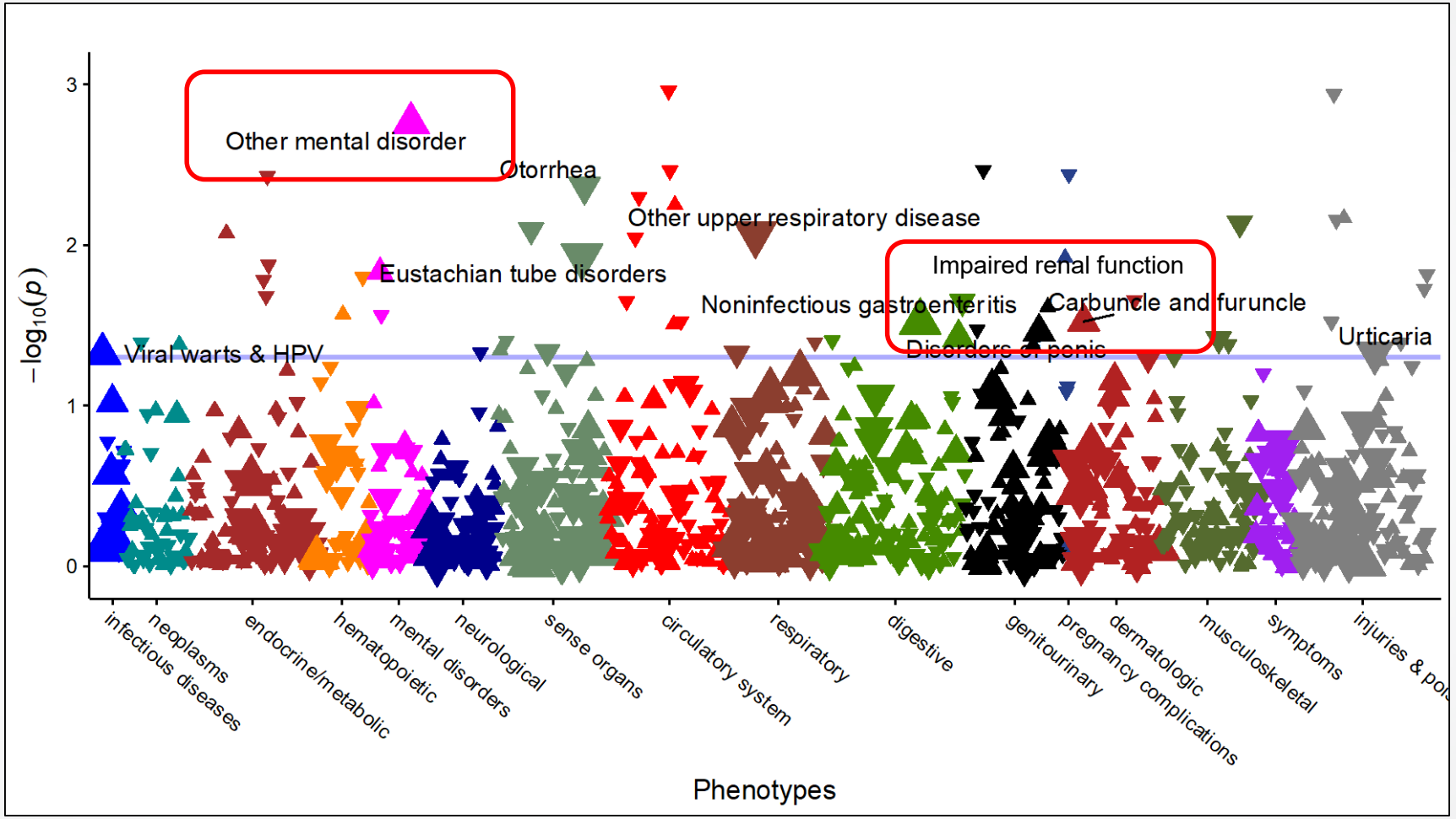
- Adjust by demographics
- Logistic regression using maximum likelihood (Wald)

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



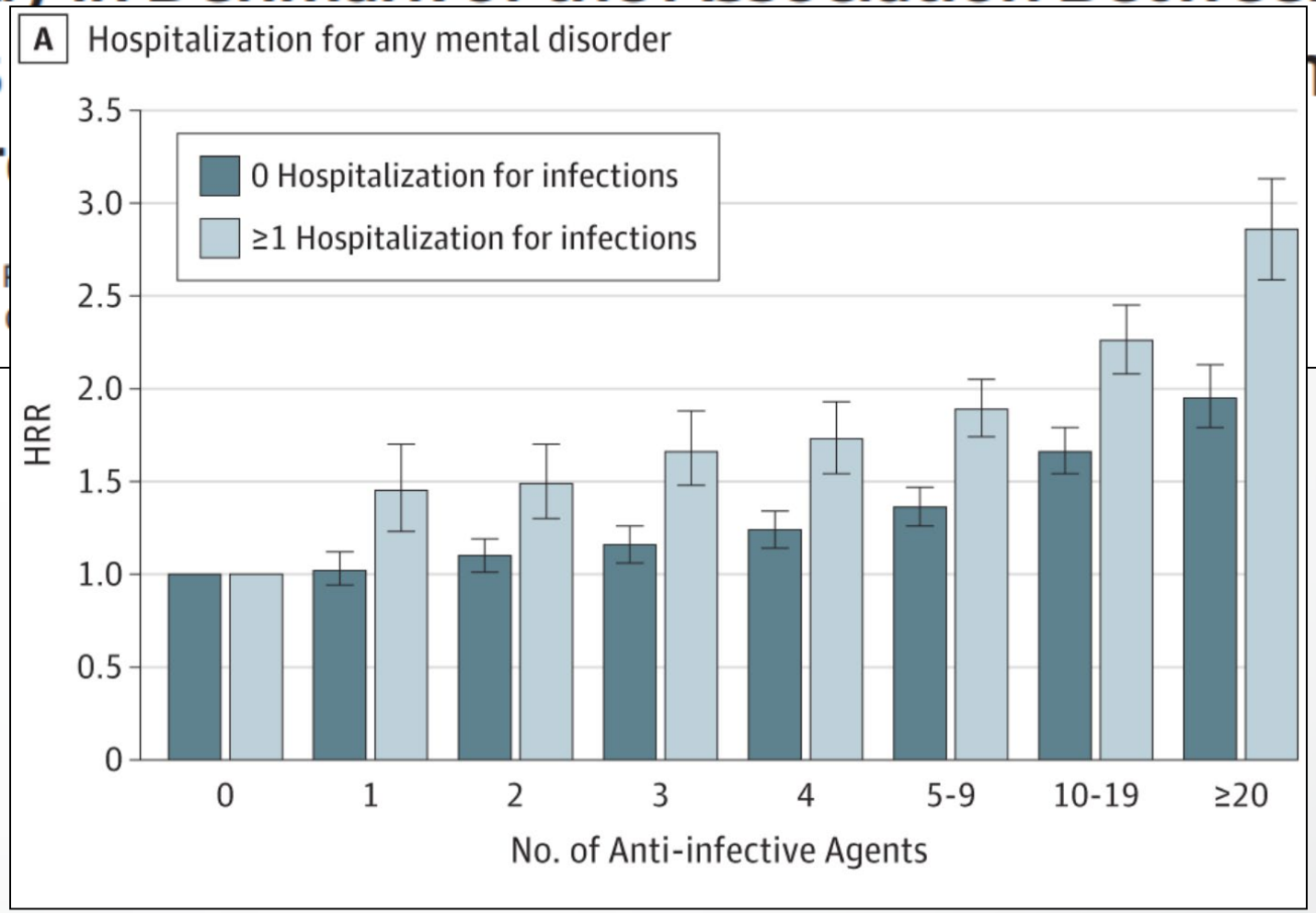
Choi et al. *Bioinformatics* 2018

New results validate the PheRS approach

JAMA Psychiatry | Original Investigation

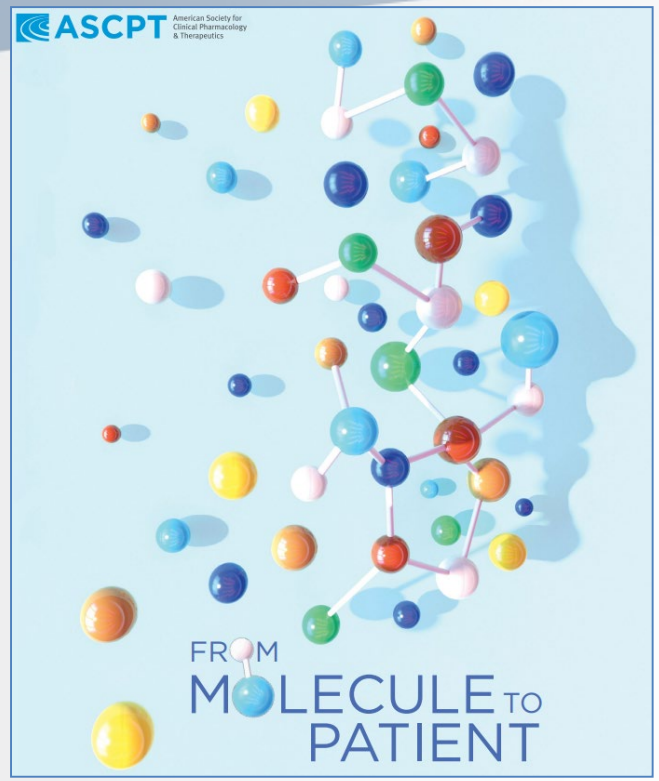
A Nationwide Study in Denmark of the Association Between Treated Infections ntal Disorders in Childr

Ole Köhler-Forsberg, MD; Liselotte Petersen,
Soren Dalsgaard, PhD; Robert H. Yolken, MD;



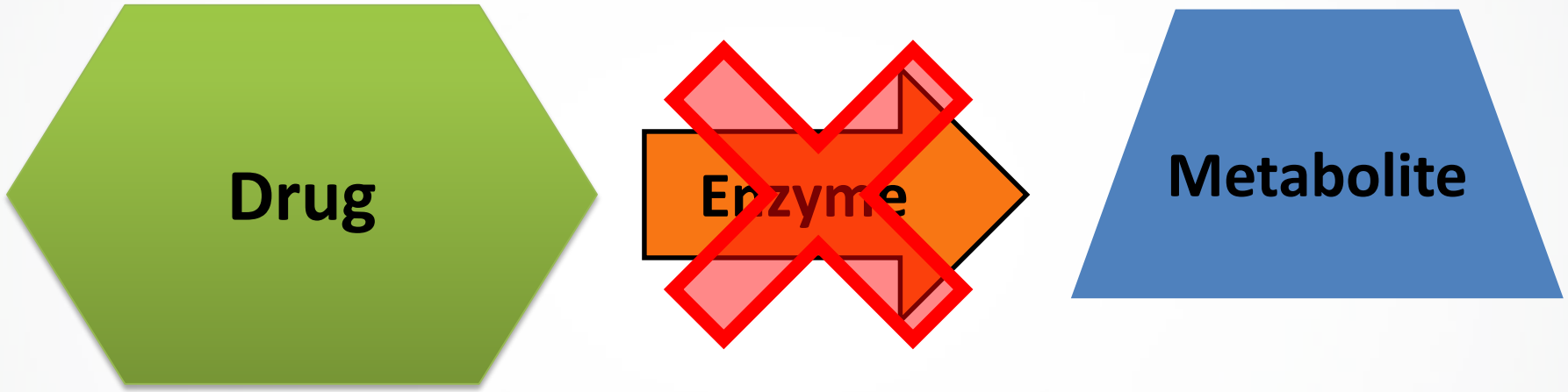
Kohler-Forsberg et al. *JAMA Psychiatry* 2018

Using Big Clinical Data for Small (Pediatric) Patients

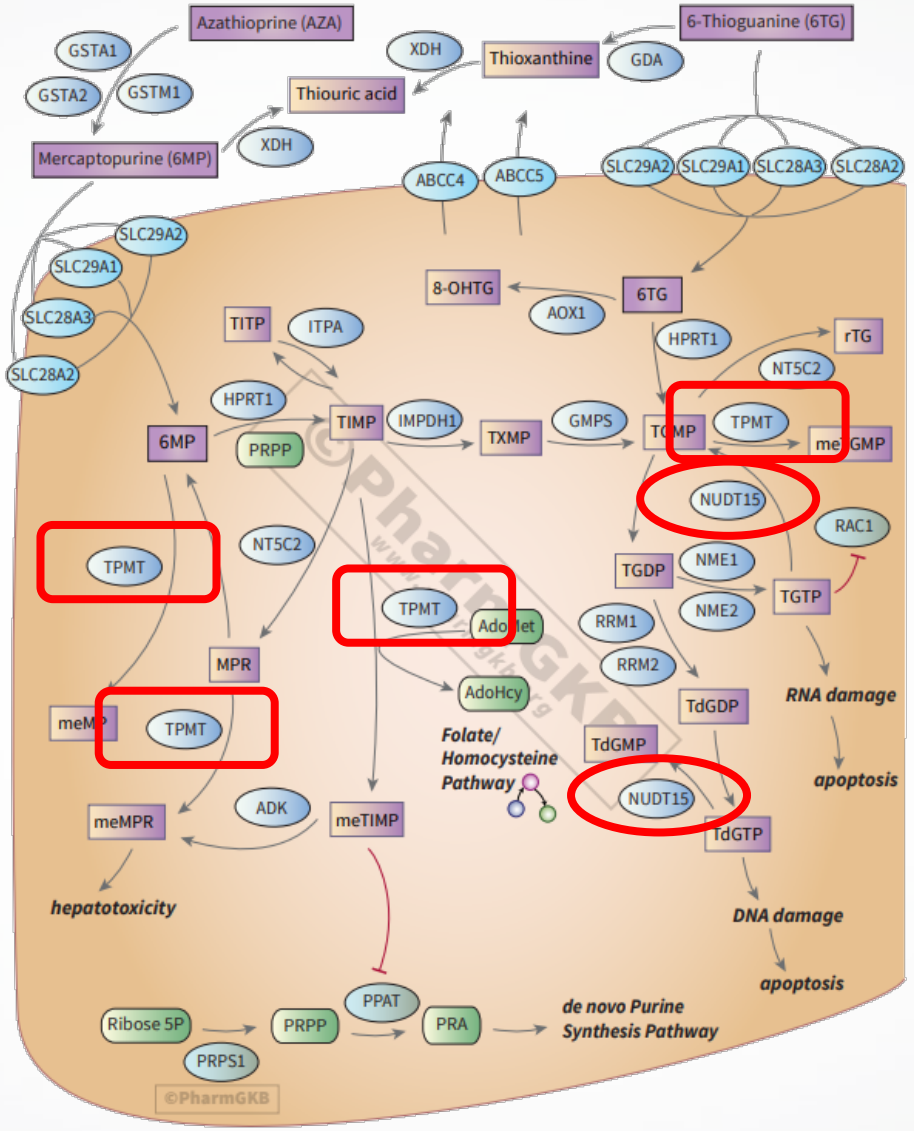


- Acute Kidney Injury
- Latent Drug Outcomes
- Drug-Gene Interactions

Genes influence drug response through drug metabolism (and other ways)



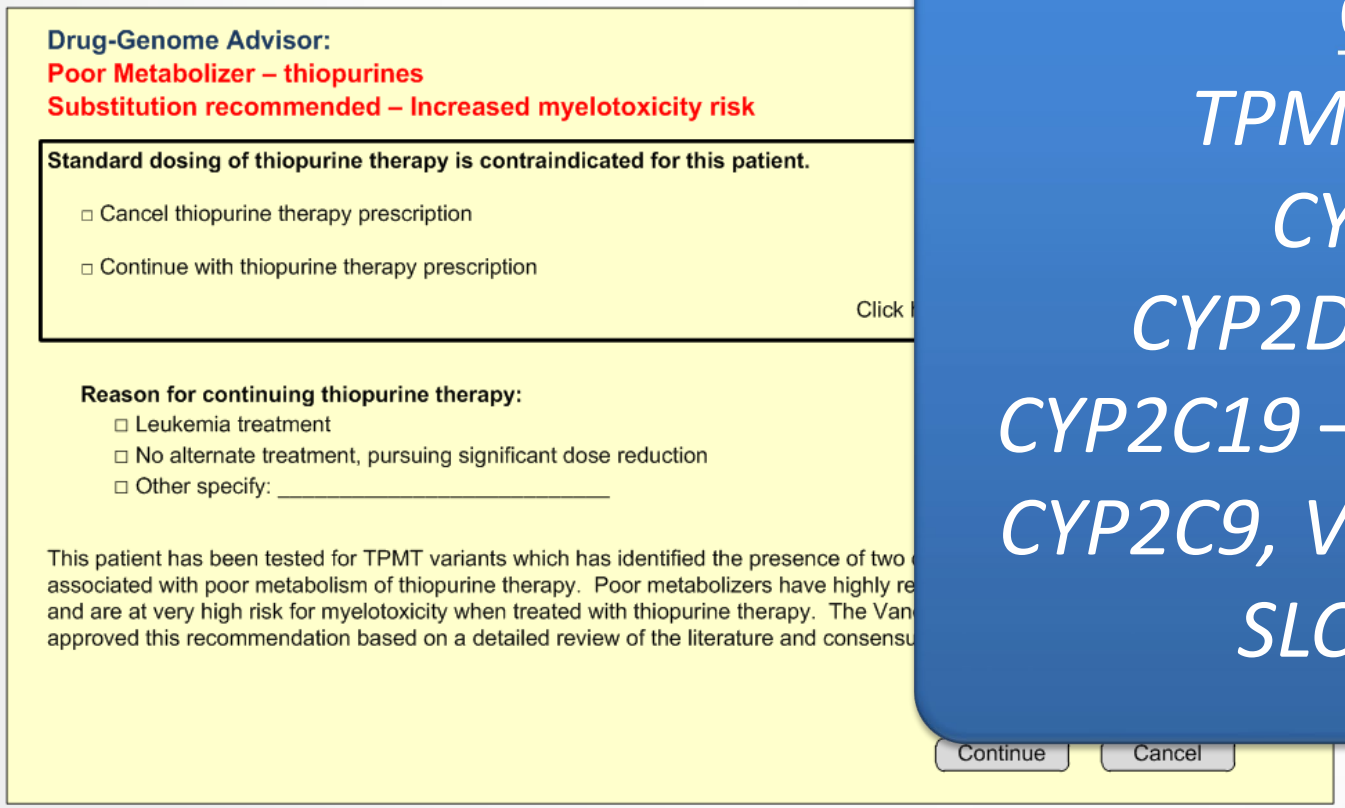
Thiopurine metabolism depends on TPMT & NUDT15



Gianluigi et al, *Pharmacogenet Genomics* 2010

PREDICT

Pharmacogenomic (PGx) Resource For Enhanced Decisions In Care & Treatment



Current Platform

TPMT – Thiopurine Drugs

CYP3A5 – Tacrolimus

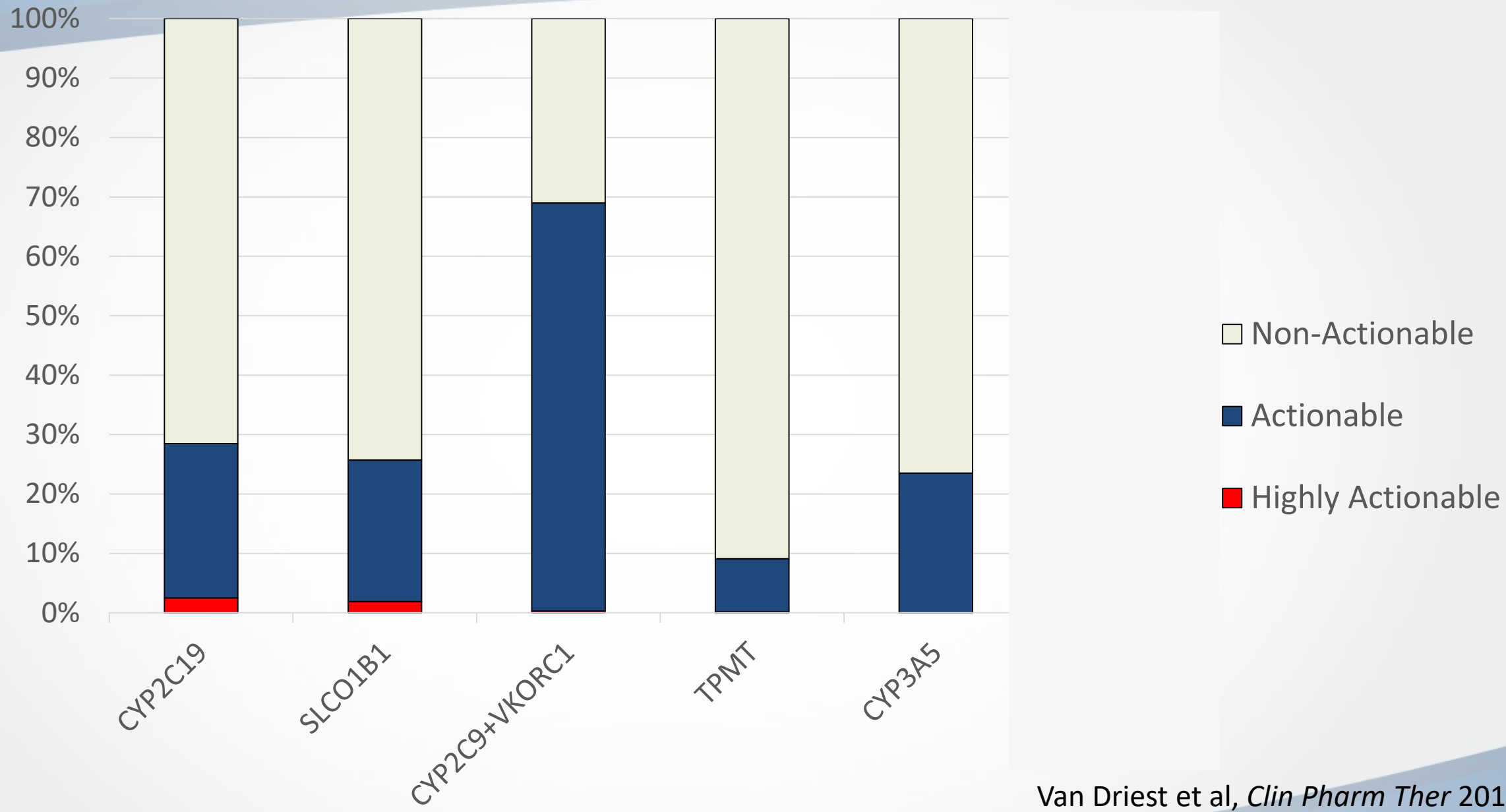
CYP2D6 – Codeine, Tramadol

CYP2C19 – Clopidogrel, Voriconazole

CYP2C9, VKORC1, CYP4F2 – Warfarin

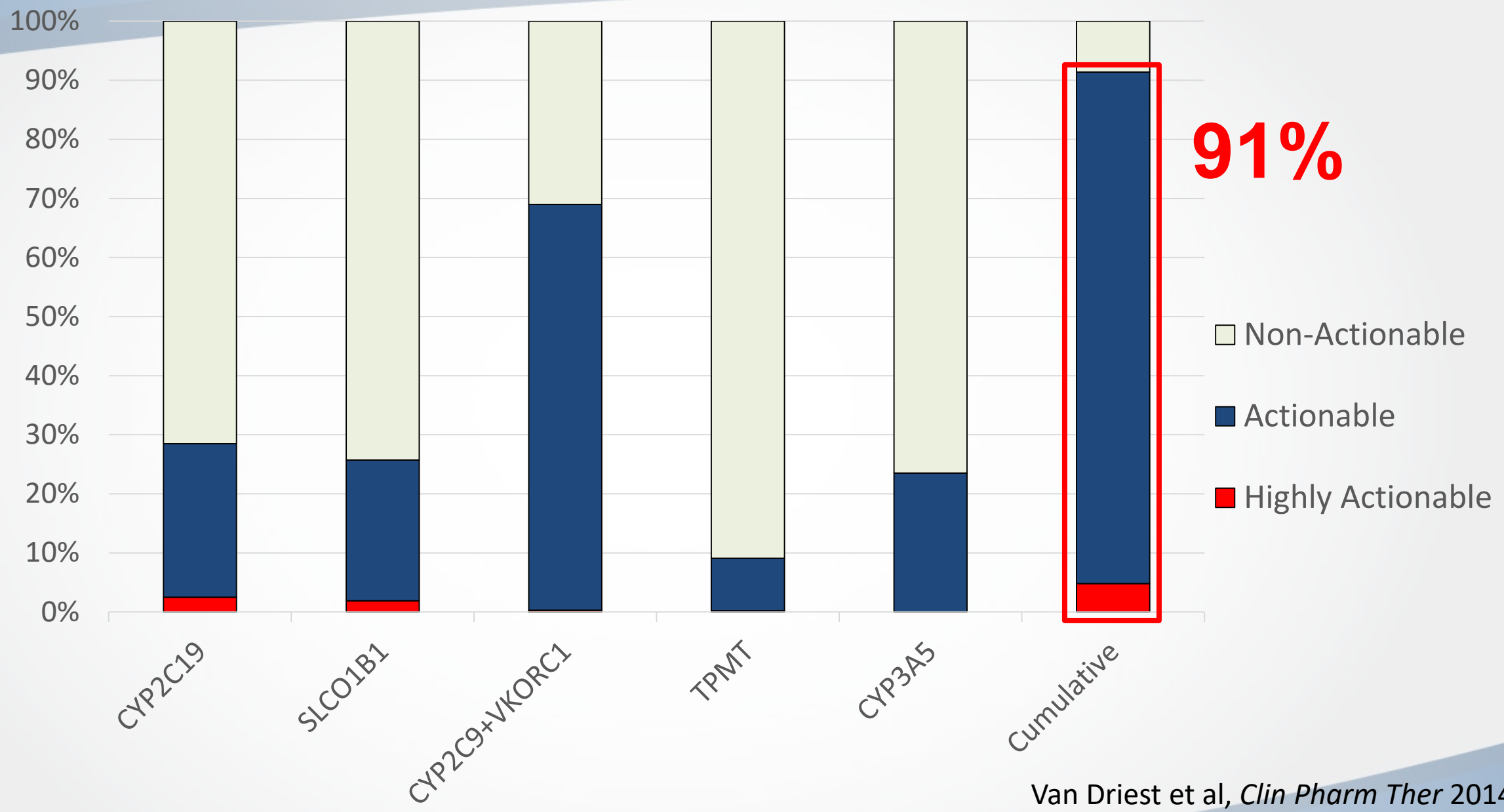
SLCO1B1 – Simvastatin

Actionable pharmaco-genotypes are common



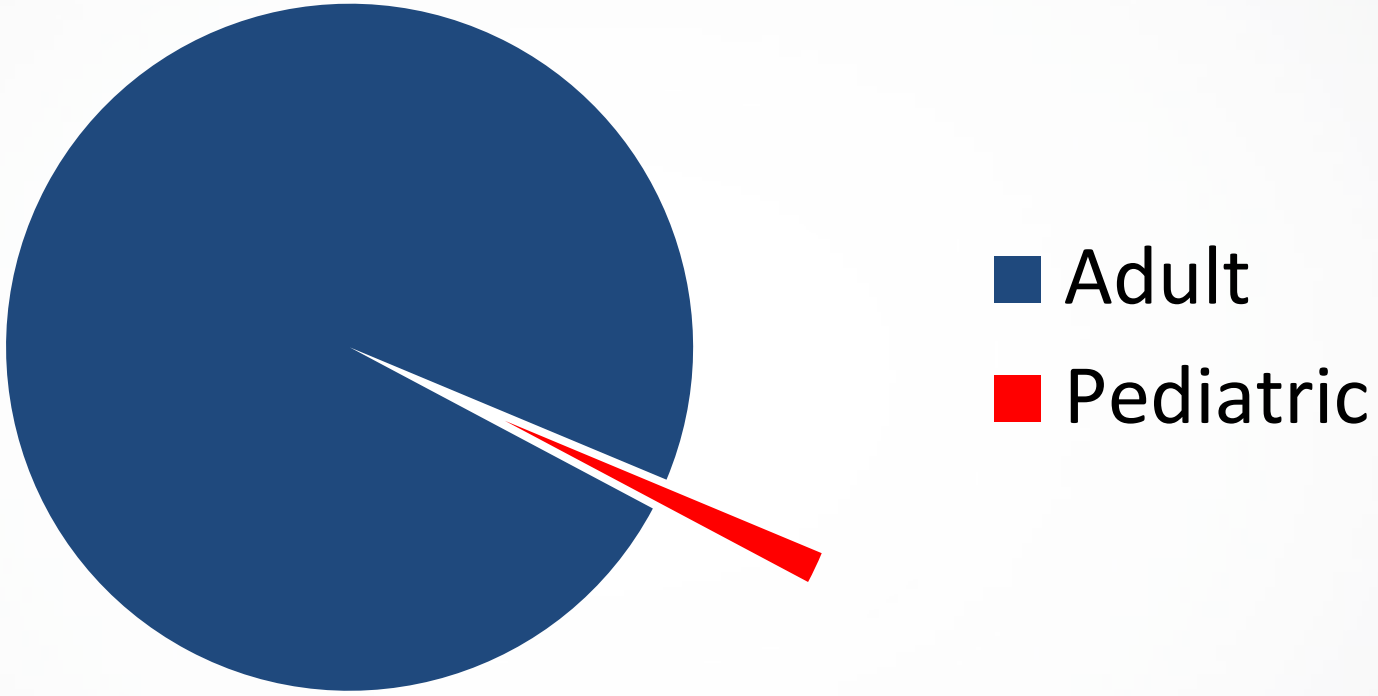
Van Driest et al, *Clin Pharm Ther* 2014

Actionable pharmaco-genotypes are common



Van Driest et al, *Clin Pharm Ther* 2014

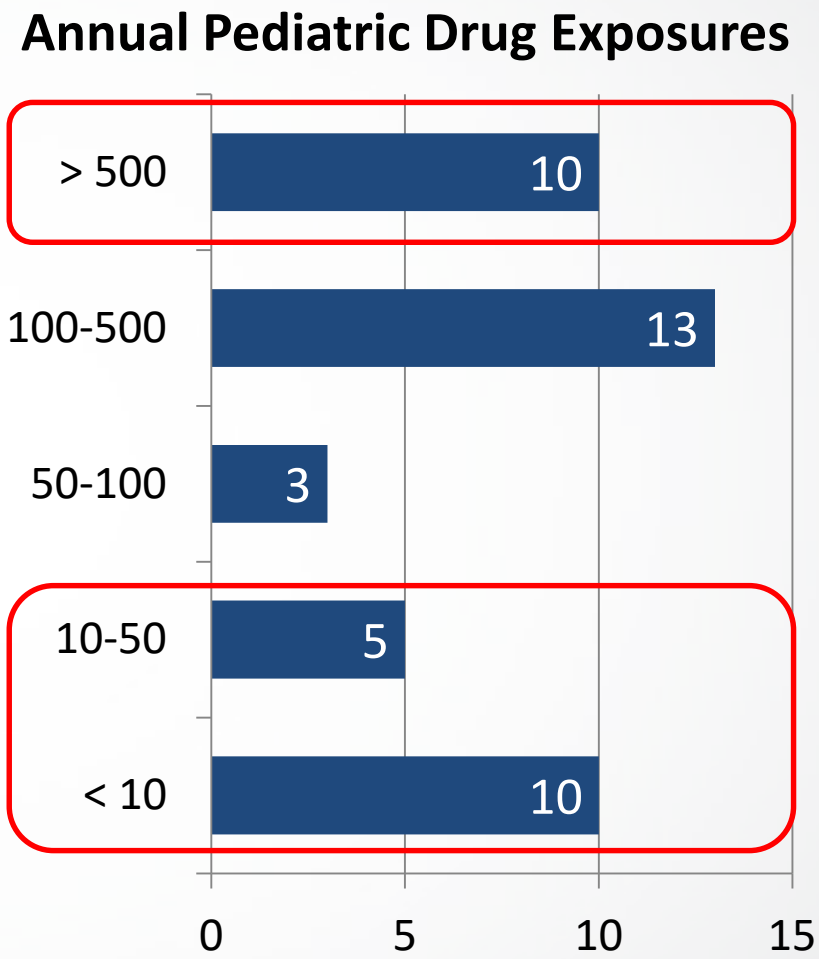
Few pediatric patients undergo PGx testing



Pediatric Exposures to “PGx drugs”

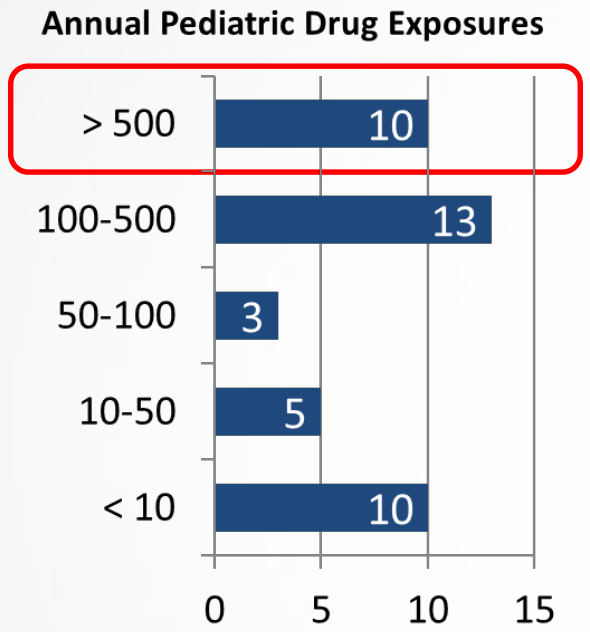
41 Drugs with known PGx

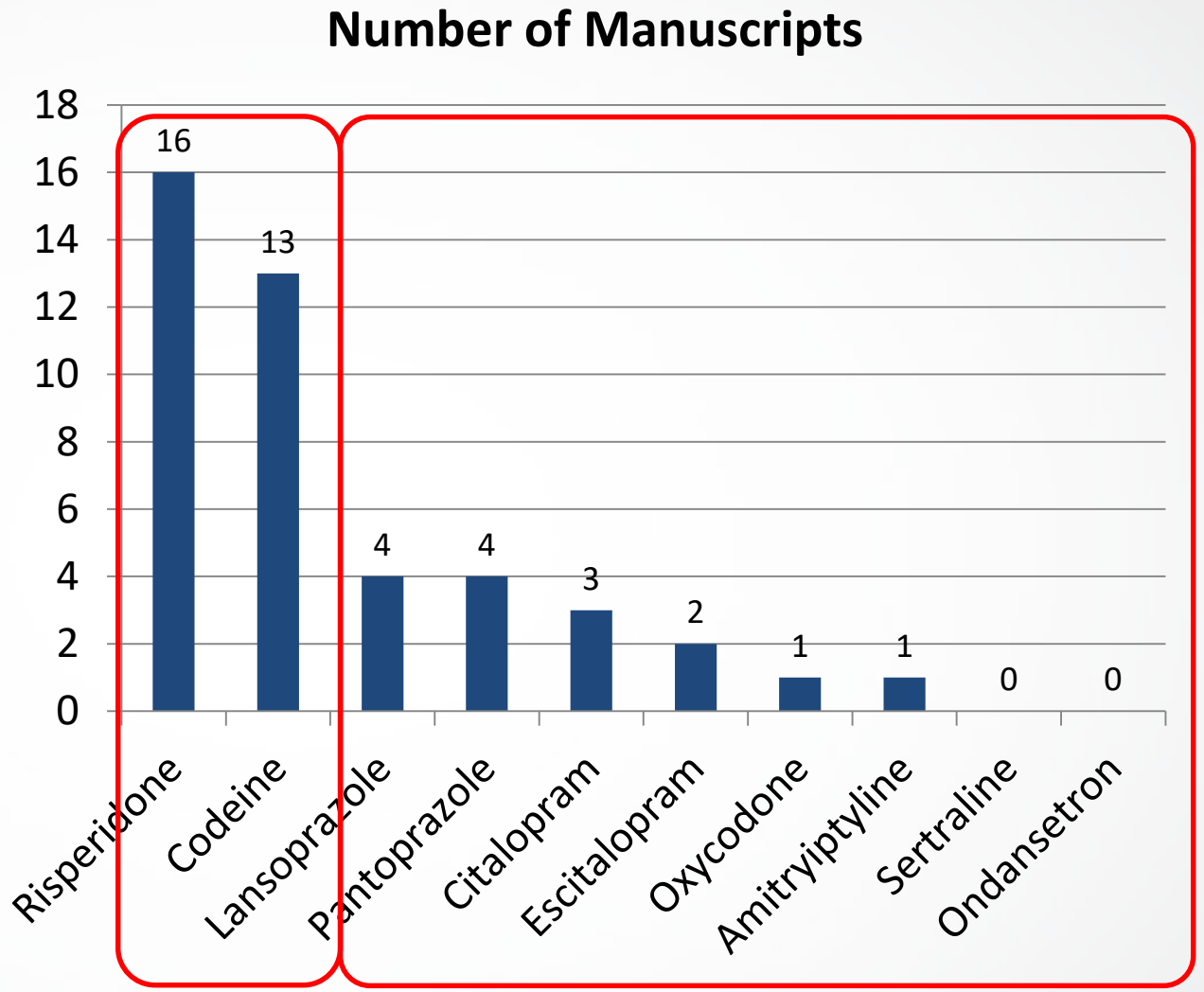
De-identified EHR: 10 years of pediatric exposures



Aka, et al. *J Personalized Med* 2017

Which PGx associations have pediatric evidence?





Aka, et al. *J Personalized Med* 2017

Why aren't we doing PGx testing for risperidone?

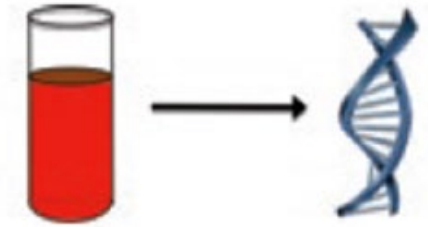
Drug	Gene	Variant(s) Assayed	Population	n	Significant Result
Risperidone	*CYP2D6*	*3–*7, duplication	5–17-year-olds with pervasive developmental disorder	25	Yes
Risperidone	*CYP2D6*	*3–*5, duplication	4–15-year-olds treated with risperidone for psychiatric or neurodevelopmental conditions	19	No
Risperidone	*CYP2D6*	*3–*6, duplication	3–21-year-olds with ASD	45	Yes
Risperidone	*CYP2D6*	*2–*11, *14, *15, *17–*20, *40–*42, duplication	3–18-year-olds treated with risperidone for a neuropsychiatric disorder	28	No
Risperidone	*CYP2D6*	*3, *4, *5, *6, duplication	10–19-year-old males with ASD or disruptive behavior disorders	47	No
Risperidone	*CYP2D6*	*3, *4, *5, *6, *9, *10, *41	8–89-year-olds with risperidone TDM	190	Yes
Risperidone	*CYP2D6*	*2–*11, *14, *15, *17–*20, *25, *26, *29, *30, *31, *35–*37, *40, *41, *43, *52, duplication	3–18-year-olds with ASD or pervasive developmental disorders	40	Yes
Risperidone	*CYP2D6*	*4	9–20-year-olds with schizophrenia or bipolar disorder	81	Yes
Risperidone	*CYP2D6*	*10	8–20-year-olds treated with risperidone for mental or behavioral disorder	120	No
Risperidone	*CYP2D6*	*4, *5, *10, *41	3–19-year-olds with ASD	147	No
Risperidone	*CYP2D6*	*2–*11, *15, *29, *33, *41, duplication	3–20-year-olds with ASD	84	Yes
Risperidone	*CYP2D6*	*10	8–20-year-olds treated with risperidone for mental and behavioral disorders	120	Yes
Risperidone	*CYP2D6*	*3–*6, *9, *10, *41, duplication	9–93-year-olds with risperidone TDM	425	Yes
Risperidone	*CYP2D6*	Affymetrix DMET Plus GeneChip microarray	Children with ASD (median age 8.8 (IQR 3.4–18.6) years)	102	Yes
Risperidone	*CYP2D6*	*4, *5, *10, *41	Children with ASD (median age 10 (IQR 7–12.15) years)	97	Yes

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

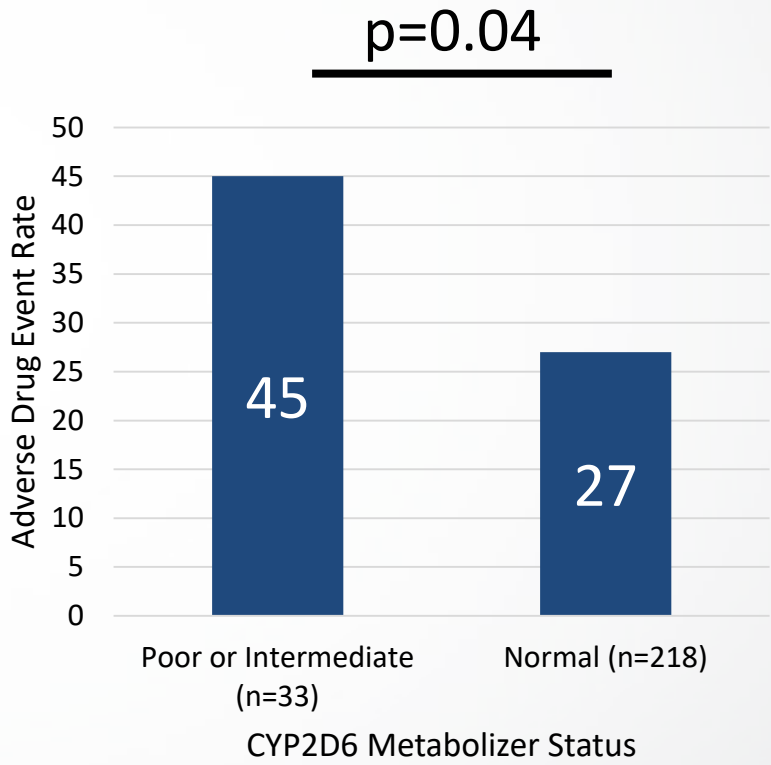
>30,000 pediatric

CYP2D6 status is associated with risperidone adverse events

Cohort Summary Characteristics	
Variable	**N=257**
Age (Years)	8.3 (6.3-10.5)
Male Sex	188 (73%)
Adverse Events	76 (30%)
Metabolizer Status	
Ultrarapid	6 (2%)
Normal	218 (85%)
Intermediate	18 (7%)
Poor	15 (6%)

Number (%) or Median (Interquartile Range)

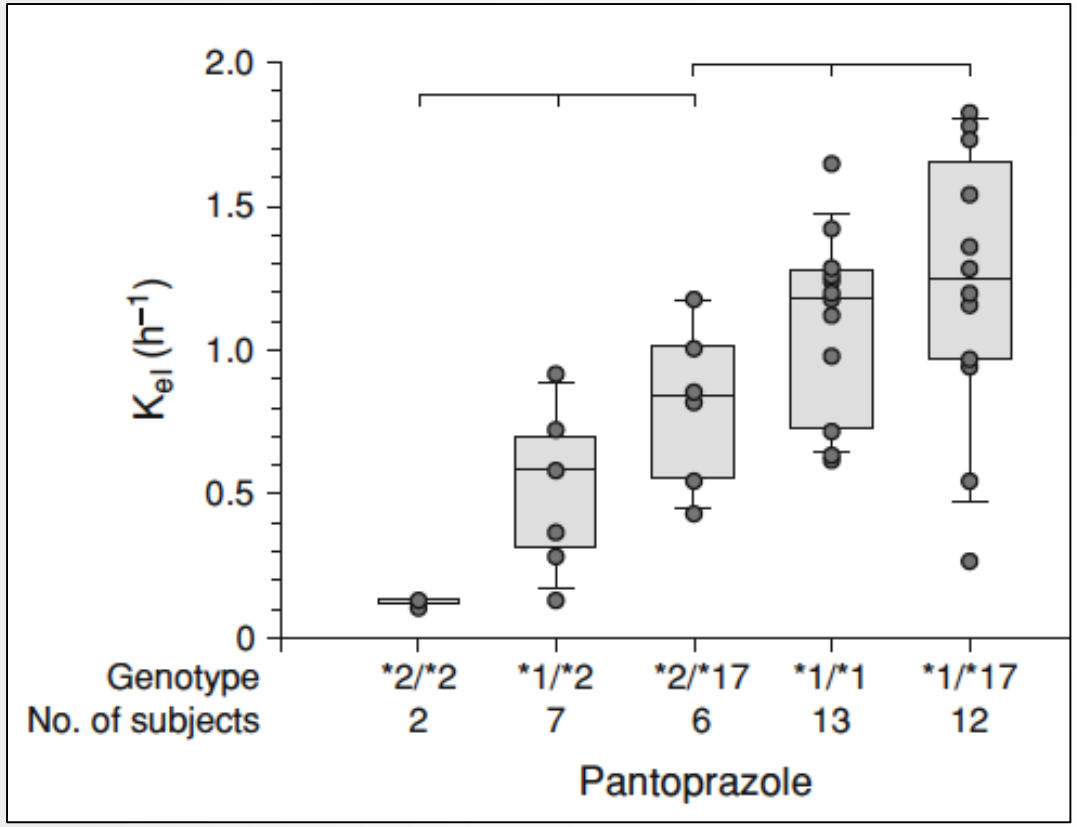
Univariate Analysis of Adverse Drug Events in 251 Children

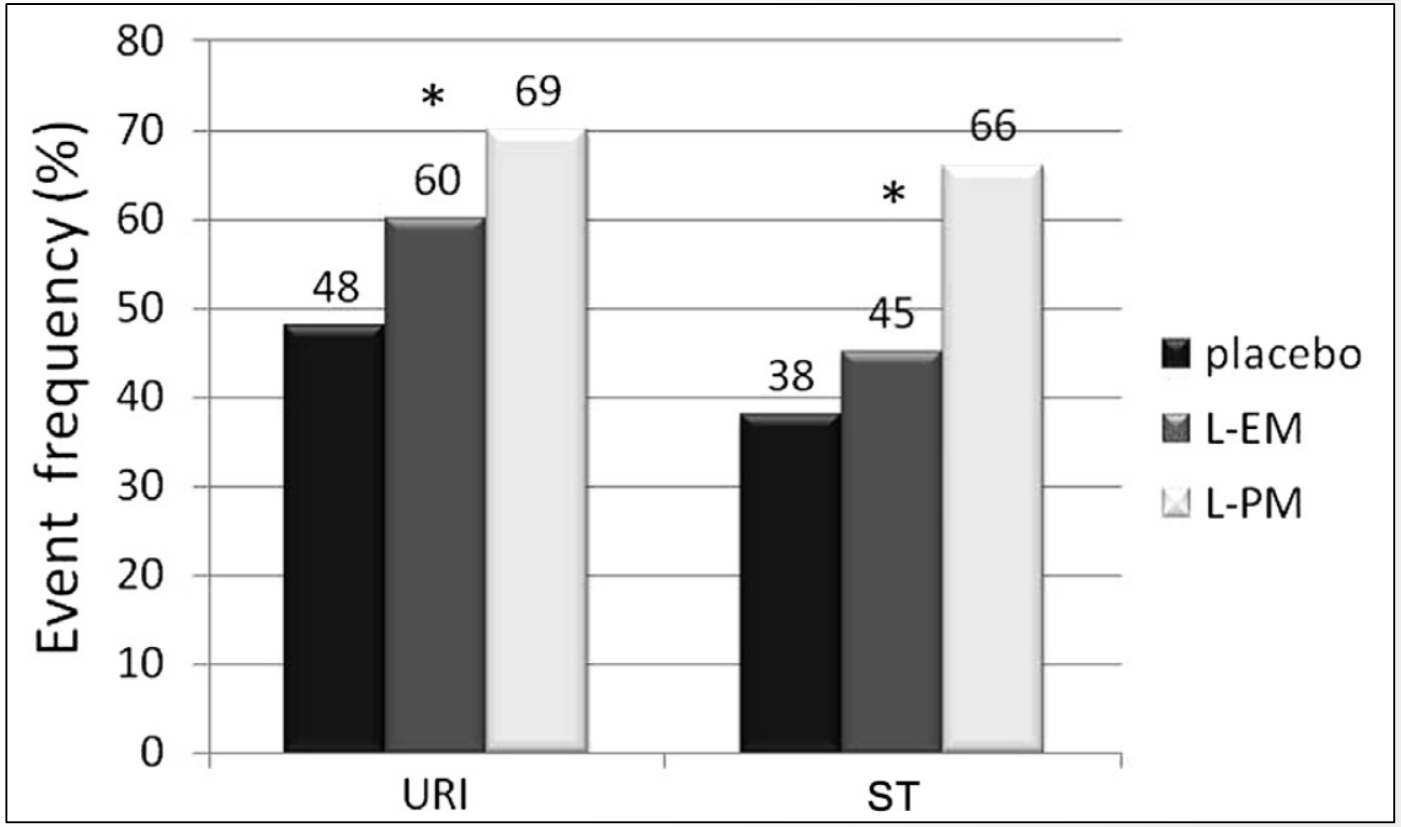


Neely et al. PIII-092

Oshikoya et al. *Pediatric Res* 2019

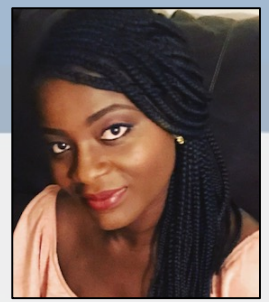
Proton Pump Inhibitor PGx





Ward & Kearns. *Pediatric Drugs* 2013
Lima et al. *J Pediatrics* 2013

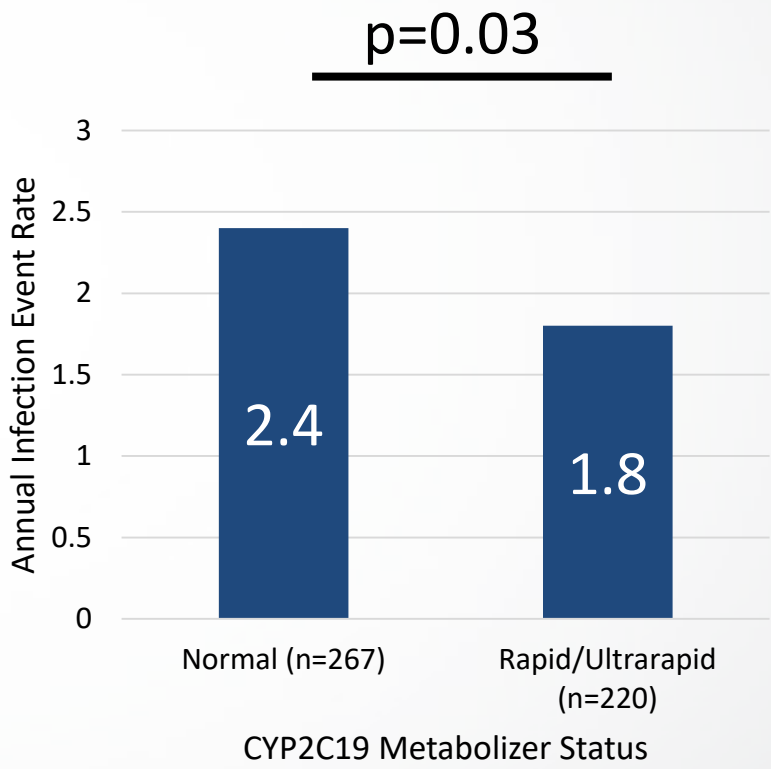
CYP2C19 status is associated with PPI adverse events



Cohort Summary Characteristics	
Variable	**N=670**
Age (Months)	7 (3-13)
Male Sex	378 (56%)
Annual Infection Events (per person)	2.1
Metabolizer Status	
Rapid/Ultrarapid	220 (33%)
Normal	267 (40%)
Intermediate/Poor	183 (27%)

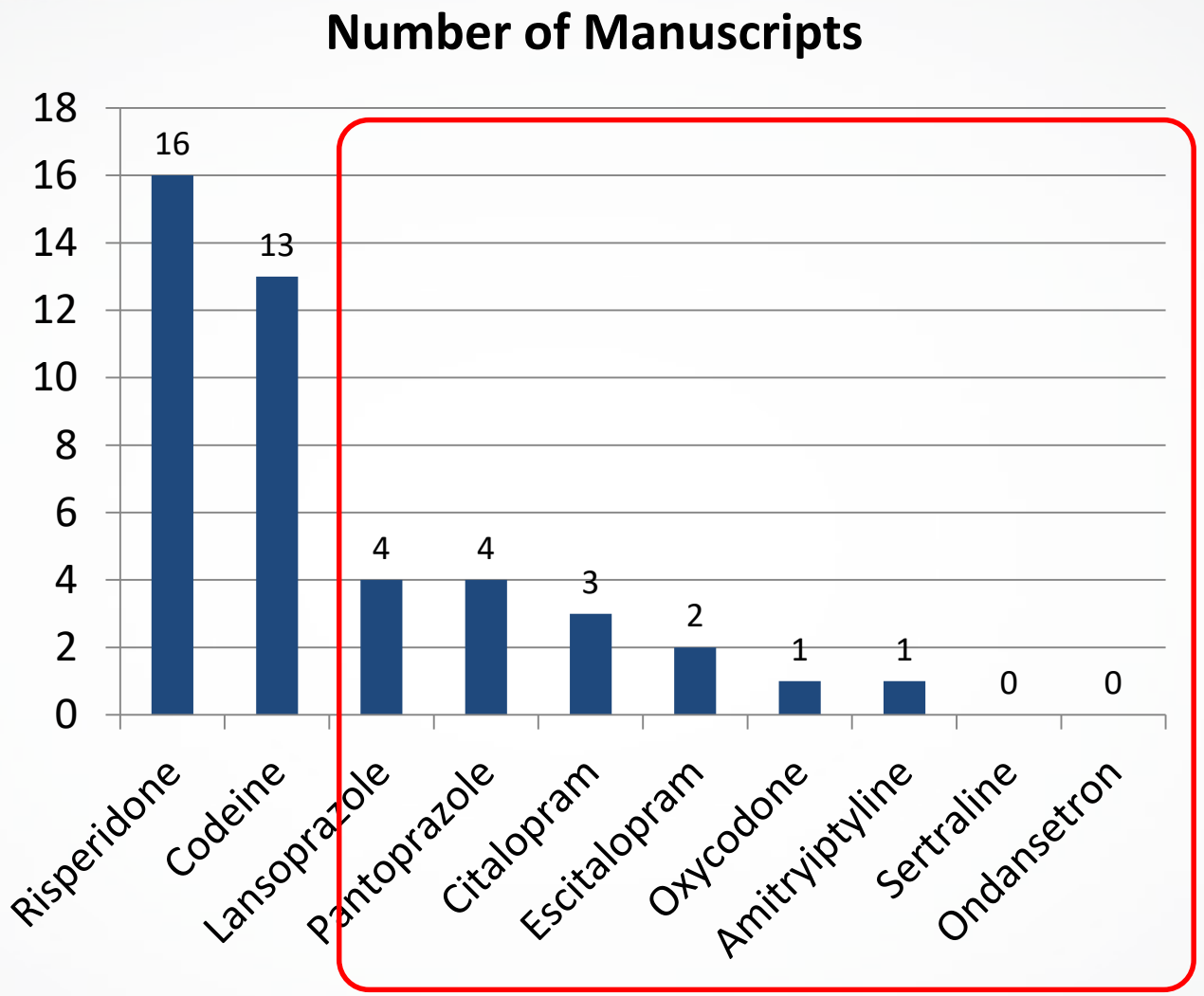
Number (%) or Median (Interquartile Range)

Univariate Analysis of Infection Events in 670 Children



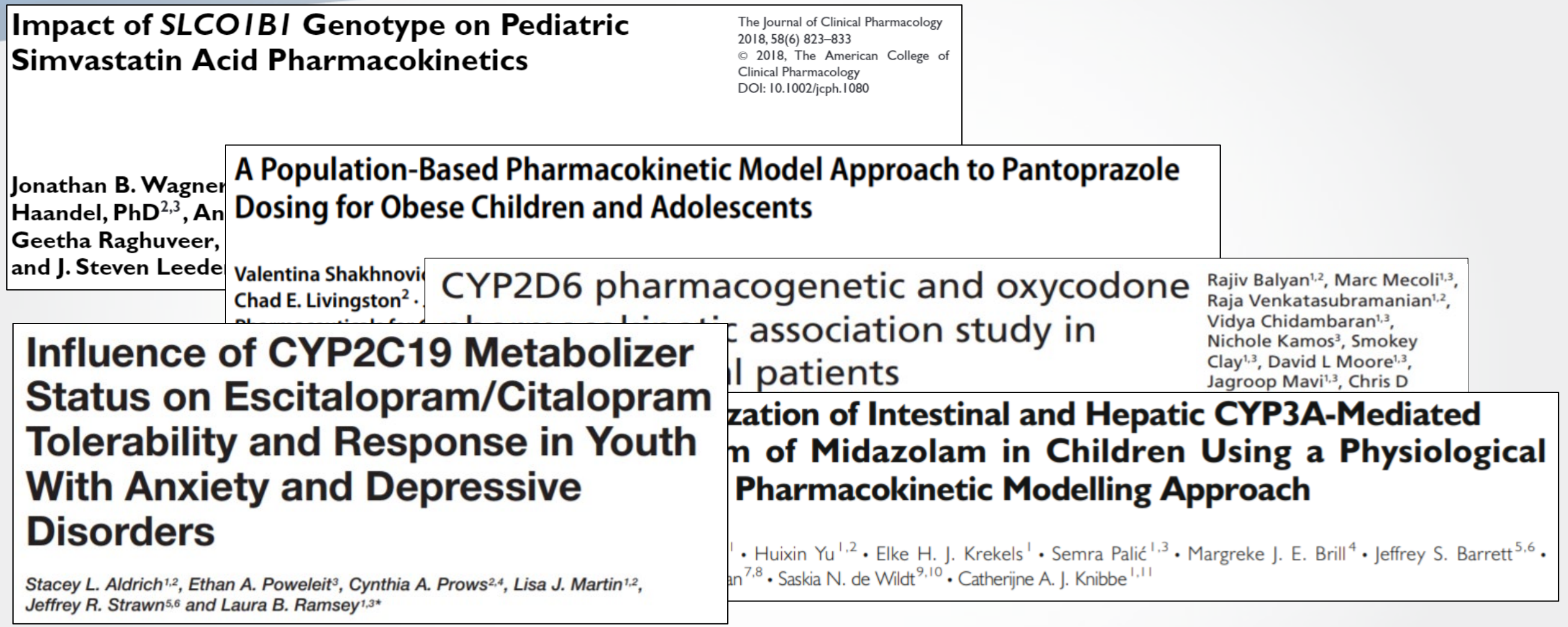
Bernal et al. PAS 2018

We continue to build evidence for pediatric PGx



Aka, et al. *J Personalized Med* 2017

Making progress in pediatric PGx



Impact of *SLCO1B1* Genotype on Pediatric Simvastatin Acid Pharmacokinetics

The Journal of Clinical Pharmacology
2018, 58(6) 823–833

DOI: 10.1002/jcph.1080

Jonathan B. Wagner
Haandel, PhD[2,3], An
Geetha Raghuveer,
and J. Steven Leede

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

Valentina Shakhnovi
Chad E. Livingston[2] ·

CYP2D6 pharmacogenetic and oxycodone
c association study in
l patients

Rajiv Balyan[1,2], Marc Mecoli[1,3], Raja Venkatasubramanian[1,2], Vidya Chidambaran[1,3], Nichole Kamos[3], Smokey Clay[1,3], David L Moore[1,3], Jagroop Mavi[1,3], Chris D

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

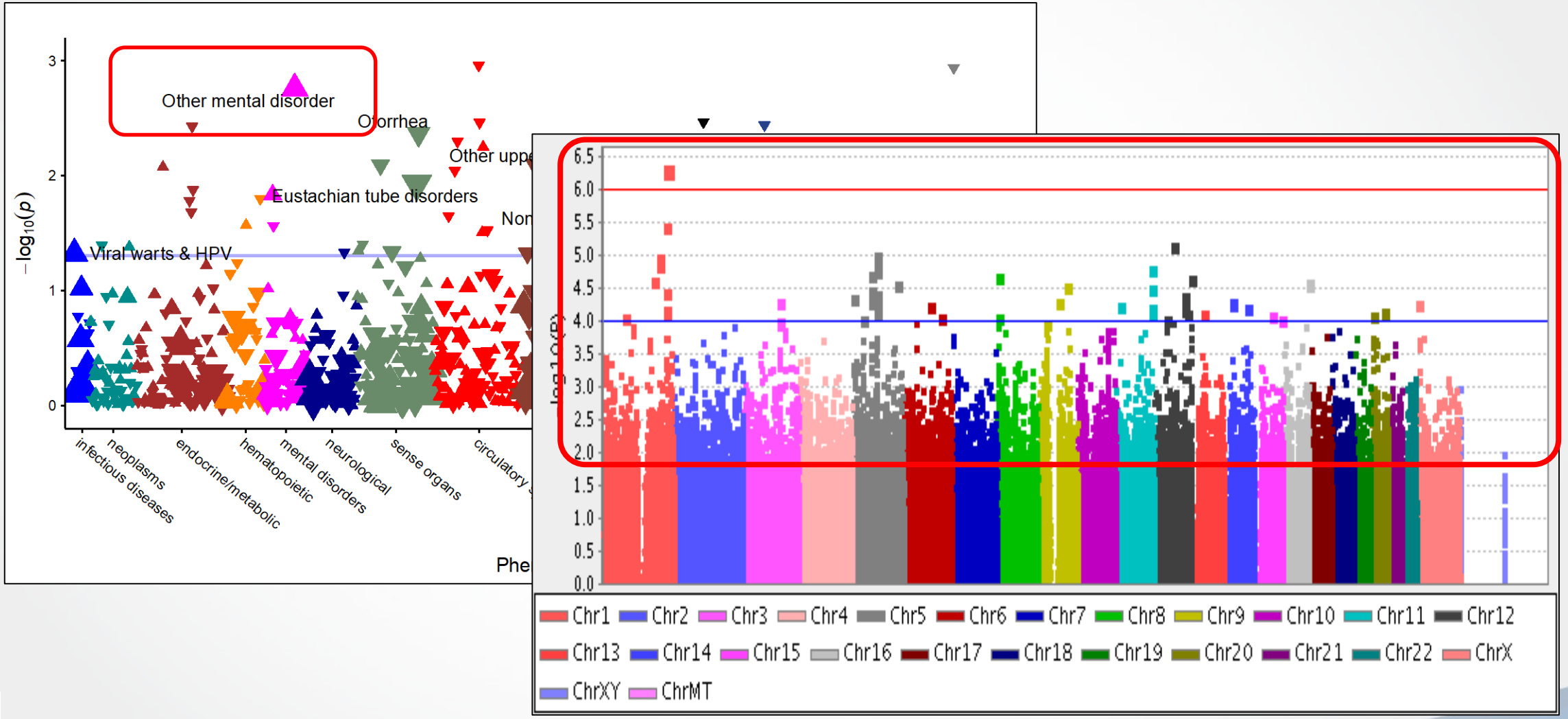
Stacey L. Aldrich[1,2], Ethan A. Poweleit[3], Cynthia A. Prows[2,4], Lisa J. Martin[1,2], Jeffrey R. Strawn[5,6] and Laura B. Ramsey[1,3]

**zation of Intestinal and Hepatic CYP3A-Mediated
m of Midazolam in Children Using a Physiological
Pharmacokinetic Modelling Approach**

l · Huixin Yu[1,2] · Elke H. J. Krekels[1] · Semra Palić[1,3] · Margreke J. E. Brill[4] · Jeffrey S. Barrett[5,6] ·
an[7,8] · Saskia N. de Wildt[9,10] · Catherijne A. J. Knibbe[1,11]

Wagner, et al. *J Clin Pharmacol* 2018; Shakhnovich, et al. *Ped Drugs* 2018
Balyan, et al. *Pharmacogenomics* 2018; Brussee, et al. *Pharm Res* 2018
Aldrich, et al. *Front Pharmacol* 2019

Complex genomic methods needed to study novel associations to complex phenotypes



Hope for the future…

Image: *The Wall Street Journal*, December 14, 2015

Acknowledgements

AKI Risk Prediction
- Tracy McGregor
- Deb Jones
- Geoffrey Fleming
- Brian Birch
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- Asli Weitkamp
- Chris Lehmann

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- Robert Carroll
- Jonathan Mosley

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- Katie Cook
- Jessica Gillon
- Alison Grisso
- Ritu Banerjee
- Natalia Jimenez-Truque
- Elizabeth J. Phillips

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- Darlene Fountain
- Carla Hissam

Van Driest Lab
- Kazeem Oshikoya
- Tiana Bernal
- Ida Aka
- Katelyn Neely
- Nicole Lambert

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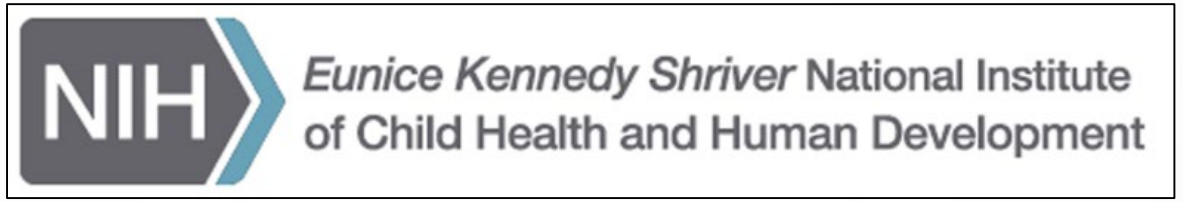
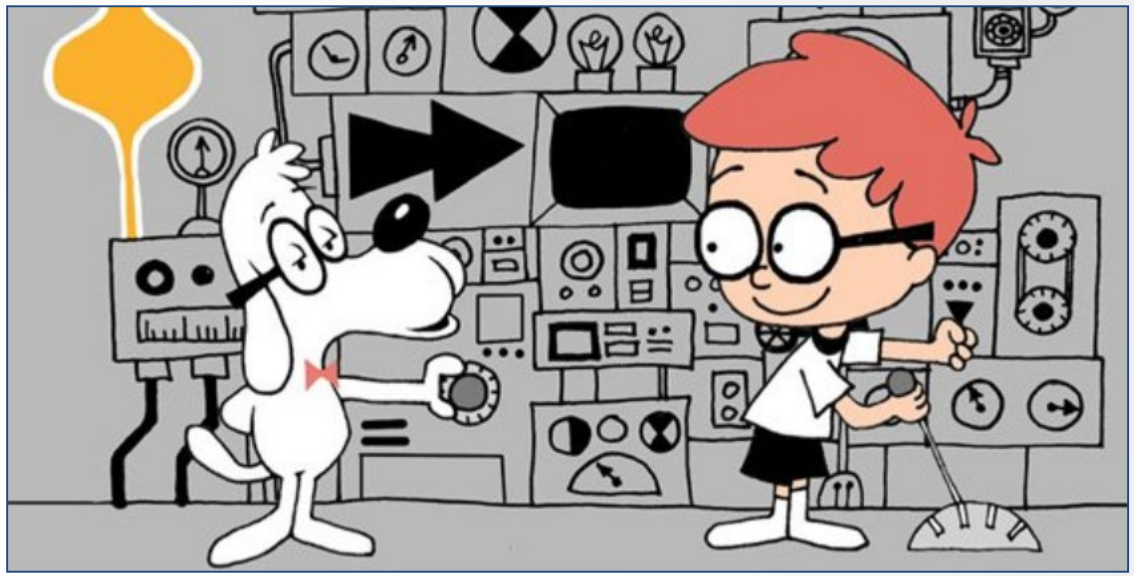
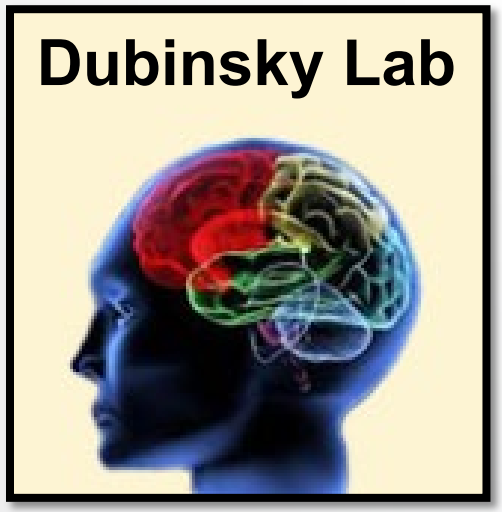
- Josh Peterson
- Cindy Vnenchek-Jones
- Jana Case
- Jill Pulley
- Cheryl Gatto

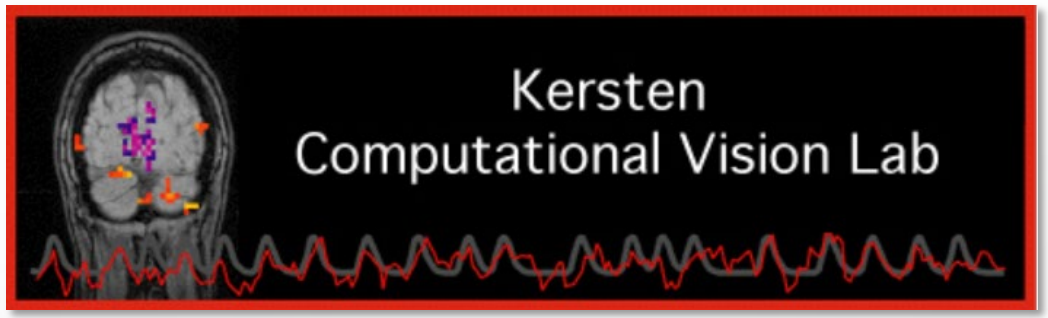
Thank you to funding agencies



Thank you to “sentinel mentors”





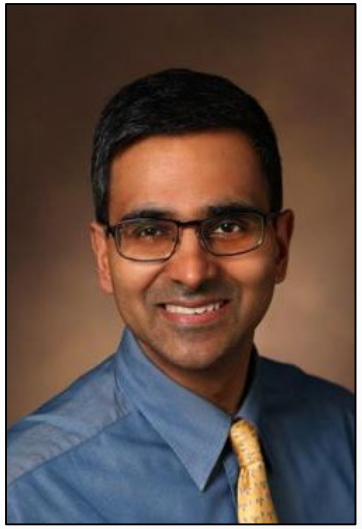


My PhD mentors

MAYO CLINIC

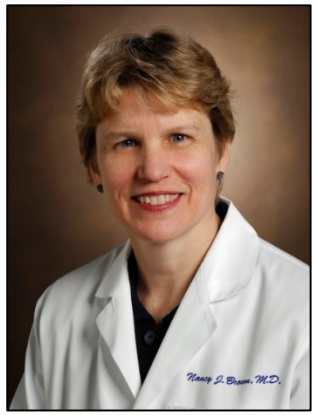
My current mentors

VANDERBILT UNIVERSITY MEDICAL CENTER

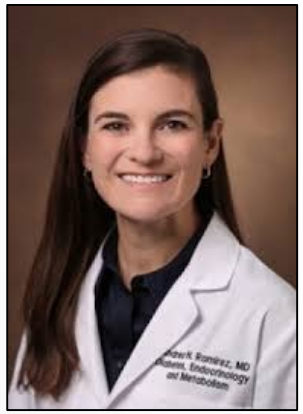


Collaboration, advice, and support











And my awesome family

Thank you for your time and attention!