Clinical Implementation of Preemptive Germline Pharmacogenetic Testing

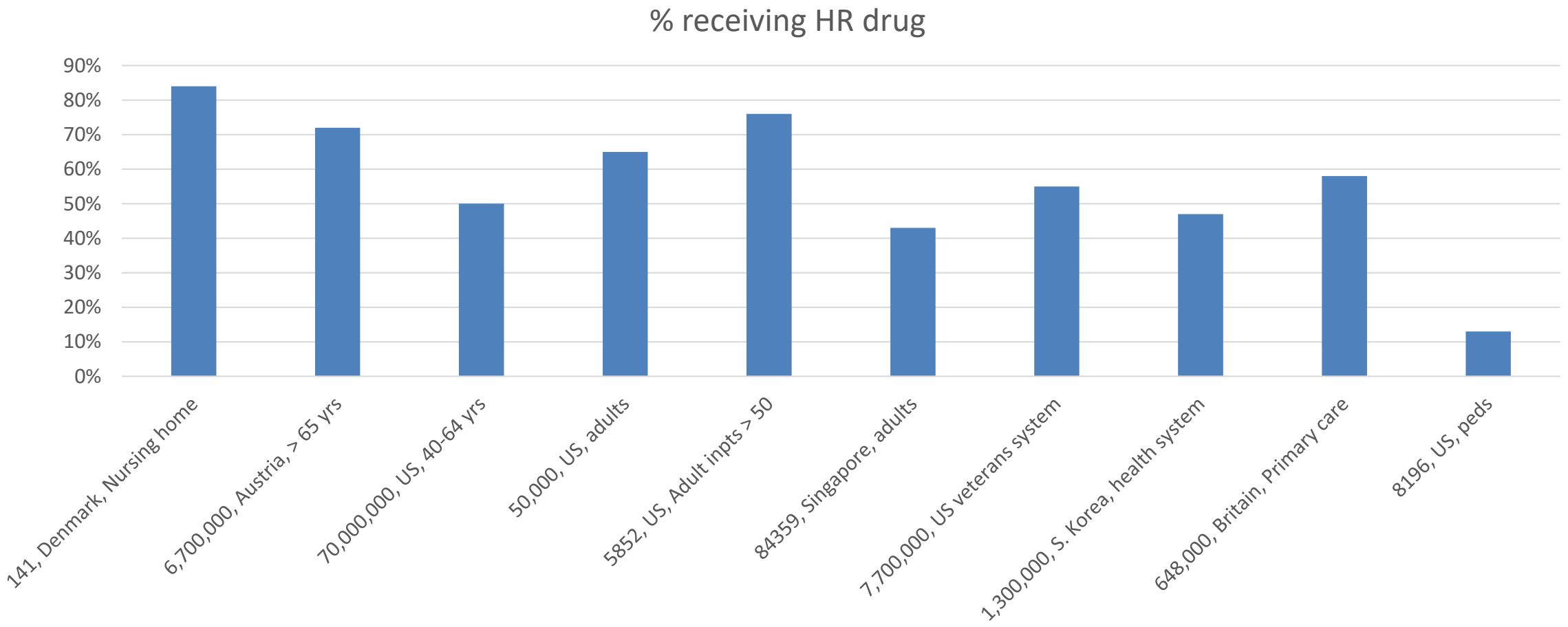
Mary V. Relling
Member, Dept of Pharmacy and Pharmaceutical Sciences

National Institutes of Health

CPIC™ Clinical Pharmacogenetics Implementation Consortium

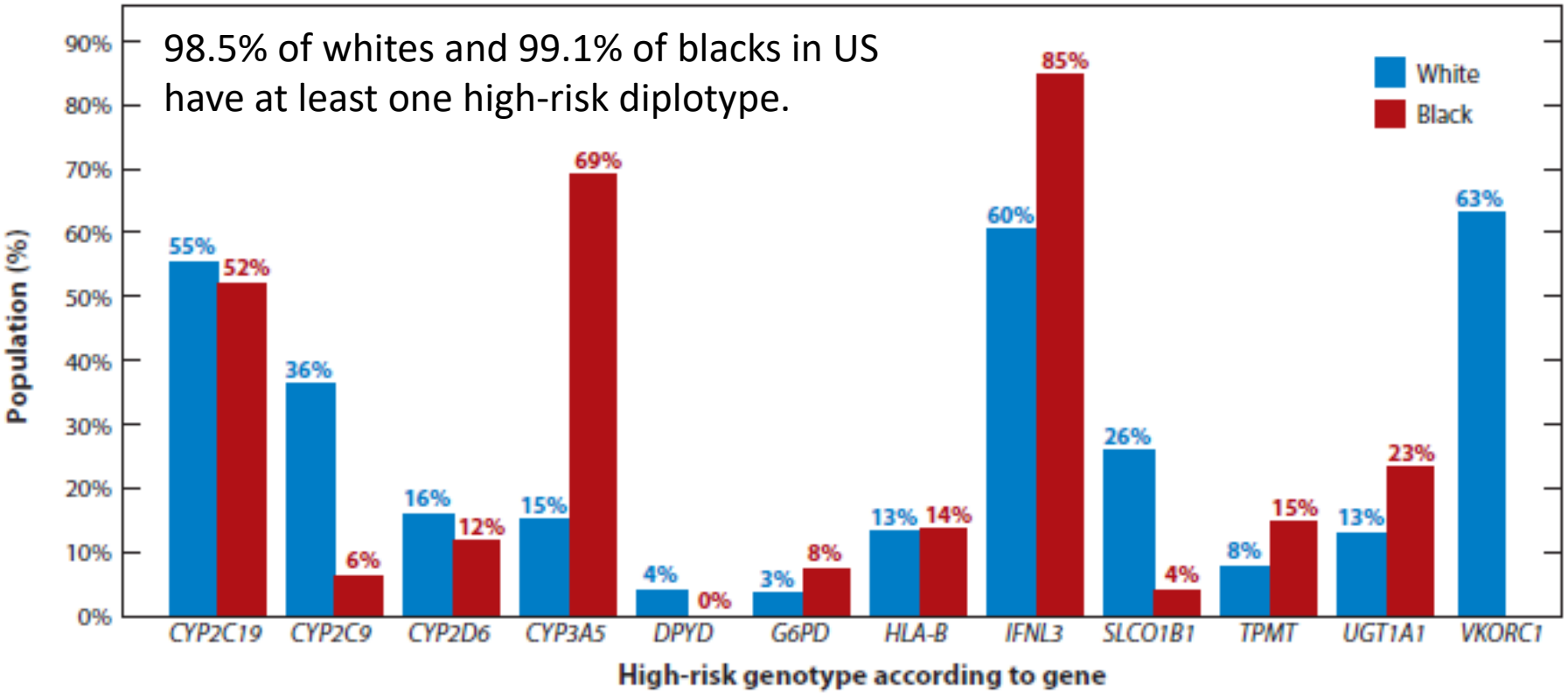
St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Most (40%-80%) adults, and many children (15%), receive at least one high-risk actionable Pgx drug



Samwald M et al. PLOS ONE 11:e0164972; Schildcrout JS, et al. Clin. Pharmacol. Ther. 92:235–42; Kuch W, et al. Stud. Health Technol. Inform. 223:253–58; Chan SL et al. Br. J. Clin. Pharmacol. 87:886–94; Kim GJ, et al. Drug Saf. 40:65–80; Vermehren C, et al J. Pers. Med. 10:78; Chanfreau-Coffinier C et al. JAMA Netw. Open 2:e195345; Kimpton JE, et al. 2019 Br. J. Clin. Pharmacol. 85:2734–46; Heise CW et al Pharmacogenet. Genom. 30:91–95; Heise CW, et al Pharmacogenet. Genom. 30:91–95

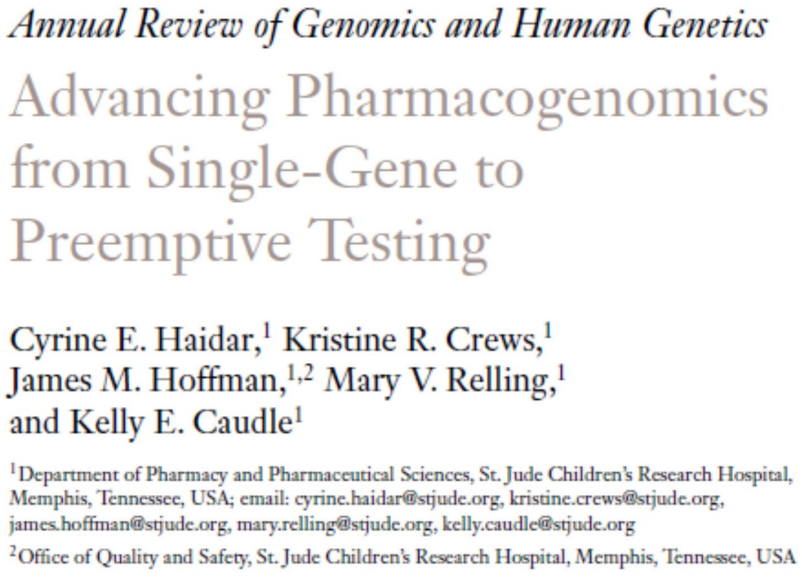
> 95% of population has high-risk diplotype for at least one of first 12 CPIC genes



Dunnenberger et al *Ann Rev Pharm Tox* 2015

So---it makes sense to do panel-based preemptive pharmacogenetic testing on everyone

- 15%-80% of people get at least one high risk drug—higher % with increased follow-up, increased age
- Collectively, > 95% of people have at least one high risk actionable genotype
- Cost of testing for “all” actionable pharmacogenes similar to cost for testing for one gene



Annual Review of Genomics and Human Genetics

Advancing Pharmacogenomics from Single-Gene to Preemptive Testing

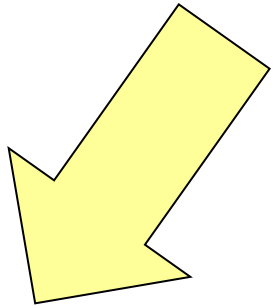
Cyrine E. Haidar,[1] Kristine R. Crews,[1] James M. Hoffman,[1,2] Mary V. Relling,[1] and Kelly E. Caudle[1]

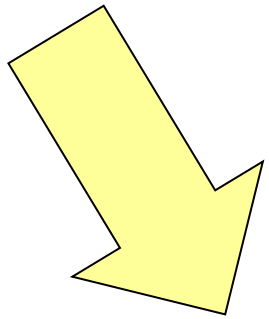
[1]Department of Pharmacy and Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; email: cyrine.haidar@stjude.org, kristine.crews@stjude.org, james.hoffman@stjude.org, mary.relling@stjude.org, kelly.caudle@stjude.org

[2]Office of Quality and Safety, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

- CPIC formed in 2009, knowing that clinical genotype data will become more and more common
- Clinicians will be faced with HOW to use clinical Pgx data
- CPIC Goal: create, curate, update, make freely available specific peer reviewed, evidence-based, updatable clinical guidelines for actionable gene/drug pairs

We are approaching implementation on 2 fronts at St. Jude





CPIC
Clinical Pharmacogenetics Implementation Consortium

St. Jude Children's Research Hospital
PG4KDS Protocol

Long-term goal: preemptive pharmacogenetic testing as the standard of care… for everyone
All CPIC guidelines.

www.stjude.org/pg4kds/implement

Funding: R24 GM115264 (Relling, Klein), then
U24 HG 010135 (Caudle, Klein)
At SJ: supports Kelly Caudle and small % of MVR, James Hoffman, Rose Gammal, April Blankenship

Why Pgx at St. Jude Children's Research Hospital?

- Mission: advance cures, and means of prevention, for pediatric catastrophic diseases through research and treatment.
- 75% of funding comes from private donors
- Comprehensive EHR, includes prescribing and dispensing
- > 90% follow-up for at least 10 years after completion therapy (our children turn into adults)
- Patients are likely (50%) to receive at least one high risk drug
- Cost of genotyping at most actionable loci is low, making multigenic, preemptive genetic testing inexpensive
- We have a culture of prescribing based on evidence and a team of qualified pharmacists
- If we can't do it….

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

PG4KDS Protocol

Clinical Implementation of Pharmacogenetics

- Opened 2011
- Goal: implement preemptive pharmacogenetic testing for all active SJ patients
- Provide CDS for at least one drug for each gene before it is implemented in the EHR
- Once a gene moves into EHR, move it in for all past and future patients
- Provide information freely to patients and others
- So far implemented:
  - 14 genes
  - 66 drugs

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Special considerations in children

- Incidental findings of Pgx results for disease risk
  - Characteristics of Incidental Findings that must be presented to patient/parent (disc w IRB)
    - Very strong association with disease risk
    - Not likely to be discovered via other means
    - Actionable before 18 yrs of age
  - Some are more likely to be discovered and/or actionable in children than adults (e.g. Klinefelter's); consent for sex chromosome findings needed up front
  - Informed consent issues
    - Parents must consent on behalf of patients
    - Parents not allowed to refuse incidental findings on behalf of their child
    - Consent must be re-obtained at age of majority
- More changes in health care systems are likely over the life of a child than the life of an elderly person (longevity of results)
- Germline genomic variants don't vary with age; every CPIC guideline has some applicability to children (no ethical reason to exclude children)
- Children become adults; most "pediatric" practice settings include patients who are "already" adults

PG4KDS: The Process

1. Patient consent

2. Blood sample

3. Genotyping (1191 genes)

4. Research database

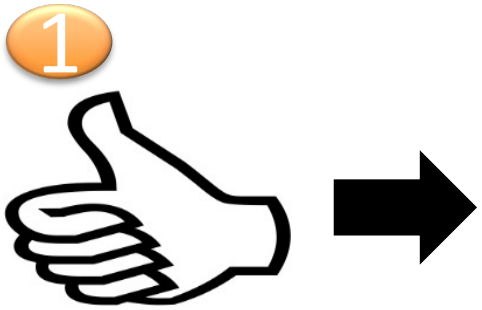
5. Select results put in EHR (14 genes)

6. Clinical decision support

7. Return of results, prescriber & patient education

Hoffman JM, et al. *Am J Med Genet C Semin Med Genet*. 2014;166C:45.

PG4KDS: The Process



Patient consent

- Research nurses retrieve daily list of all new pts
- Protocol allows research nurses to deem when and whether to approach patients
  - > 95% of patients approached consent
  - > 96% reconsent at 18 yrs of age
- Enrollment treated similarly to enrollment on tissue banking protocols
- All processes approved by Pharmacogenomics Oversight Committee, which reports to P&T and Medical Executive Committee

Hoffman JM, et al. *Am J Med Genet C Semin Med Genet*. 2014;166C:45.

PG4KDS: The Process

1. Patient consent

2. Blood sample

3. Genotyping (1191 genes)

4. Research database

5. Select results put in EHR (14 genes)

6. Clinical decision support

7. Return of results, prescriber & patient education

Hoffman JM, et al. *Am J Med Genet C Semin Med Genet*. 2014;166C:45.

PG4KDS Demographics: n =6682; nearly 47% of patients genotyped are non-white

Median age at enrollment (range)	9.4 years (0.17-51.92 years)
White—Hispanic	571
White Non-Hispanic	3558
Black--Hispanic	12
Black Non-Hispanic	2018
Asian	116
American Indian	12
Pacific Islander	6
Multi Race/Other --Hispanic	106
Non-Hispanic	283

Unpublished data from 10/3/2022

CPIC™
Clinical Pharmacogenetics Implementation Consortium

2011

- *TPMT* – thiopurines
- *CYP2C19*– clopidogrel
- *CYP2C9, VKORC*1 – warfarin

2012

- *CYP2D6* – codeine
- *HLA-B* – abacavir
- *SLCO1B1* – simvastatin

2013

- *HLA-B* – allopurinol
- *CYP2D6, CYP2C19* – TCAs
- *HLA-B* – carbamazepine
- *DPYD* -- 5FU / capecitabine
- *TPMT* – thiopurines—UPDATE
- *CYP2C19* – clopidogrel—UPDATE

2014

- *IL28B* -- PEG interferon α
- *CFTR* -- Ivacaftor
- *G6PD* -- Rasburicase
- *CYP2C9, HLA-B* -- Phenytoin
- *CYP2D6* – codeine--UPDATE
- *HLA-B* – abacavir--UPDATE
- *SLCO1B1* – simvastatin—UPDATE

2015

- *CYP3A5* – tacrolimus
- *CYP2D6*, *CYP2C19*– SSRIs
- *UGT1A1* – atazanavir
- *HLA-B* – allopurinol—UPDATE

2016

- *CYP2C19* – voriconazole
- *CYP2D6* – ondansetron
- *CYP2C9, VKORC*1 – warfarin--UPDATE
- *CYP2D6, CYP2C19* – TCAs—UPDATE

2017

- *CYP2D6* – tamoxifen
- *HLA-B* – carbamazepine—UPDATE
- *DPYD* -- 5FU / capecitabine—UPDATE

2018

- *RYR1, CACNA1S*– inhaled anesthetics
- *TPMT, NUDT15* – thiopurines—UPDATE

https://cpicpgx.org/guidelines/

2019

- *CYP2B6*—efavirenz
- *CYP2D6*—atomoxetine
- *CYP2C*--NSAIDS

2020 (including in progress)

- *CYP2C9*, HLA—phenytoin
- CY*P2C19*--PPI

2021

- *CYP2D6* - opioids
- *mtRNR1*—aminoglycosides

2022

- *SLCO1B1*-simvatatin-UPDATE
- *CYP2C19*--clopidogrel

2011

- *TPMT* – thiopurines
- *CYP2C19*– clopidogrel
- *CYP2C9, VKORC*1 – warfarin

2012

- *CYP2D6* – codeine
- *HLA-B* – abacavir
- *SLCO1B1* – simvastatin

2013

- *HLA-B* – allopurinol
- *CYP2D6, CYP2C19* – TCAs
- *HLA-B* – carbamazepine
- *DPYD* -- 5FU / capecitabine
- *TPMT* – thiopurines—UPDATE
- *CYP2C19* – clopidogrel—UPDATE

2014

- *IL28B* -- PEG interferon α
- *CFTR* -- Ivacaftor
- *G6PD* -- Rasburicase
- *CYP2C9, HLA-B* -- Phenytoin
- *CYP2D6* – codeine--UPDATE
- *HLA-B* – abacavir--UPDATE
- *SLCO1B1* – simvastatin—UPDATE

CPIC™ Clinical Pharmacogenetics Implementation Consortium

2015

- *CYP3A5* – tacrolimus
- *CYP2D6*, *CYP2C19*– SSRIs
- *UGT1A1* – atazanavir
- *HLA-B* – allopurinol—UPDATE

2016

- *CYP2C19* – voriconazole
- *CYP2D6* – ondansetron
- *CYP2C9, VKORC*1 – warfarin--UPDATE
- *CYP2D6, CYP2C19* – TCAs—UPDATE

2017

- *CYP2D6* – tamoxifen
- *HLA-B* – carbamazepine—UPDATE
- *DPYD* -- 5FU / capecitabine—UPDATE

2018

- *RYR1, CACNA1S*– inhaled anesthetics
- *TPMT, NUDT15* – thiopurines—UPDATE

https://cpicpgx.org/guidelines/

Implemented at St. Jude

2019

- *CYP2B6*—efavirenz
- *CYP2D6*—atomoxetine
- *CYP2C*--NSAIDS

2020 (including in progress)

- *CYP2C9*, HLA—phenytoin
- CY*P2C19*--PPI

2021

- *CYP2D6* - opioids
- *mtRNR1*—aminoglycosides

2022

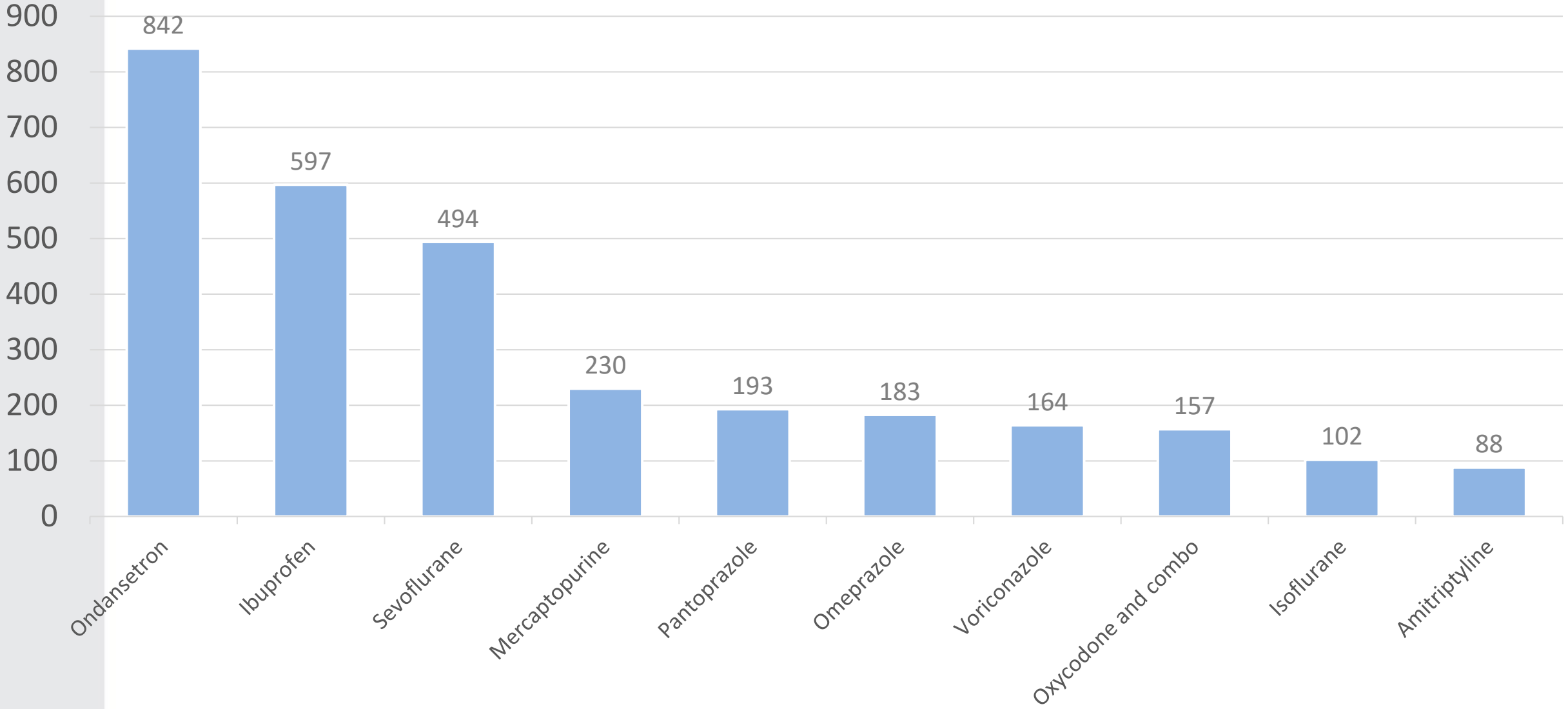
- *SLCO1B1*-simvatatin-UPDATE
- *CYP2C19*--clopidogrel

CPIC™
Clinical Pharmacogenetics Implementation Consortium

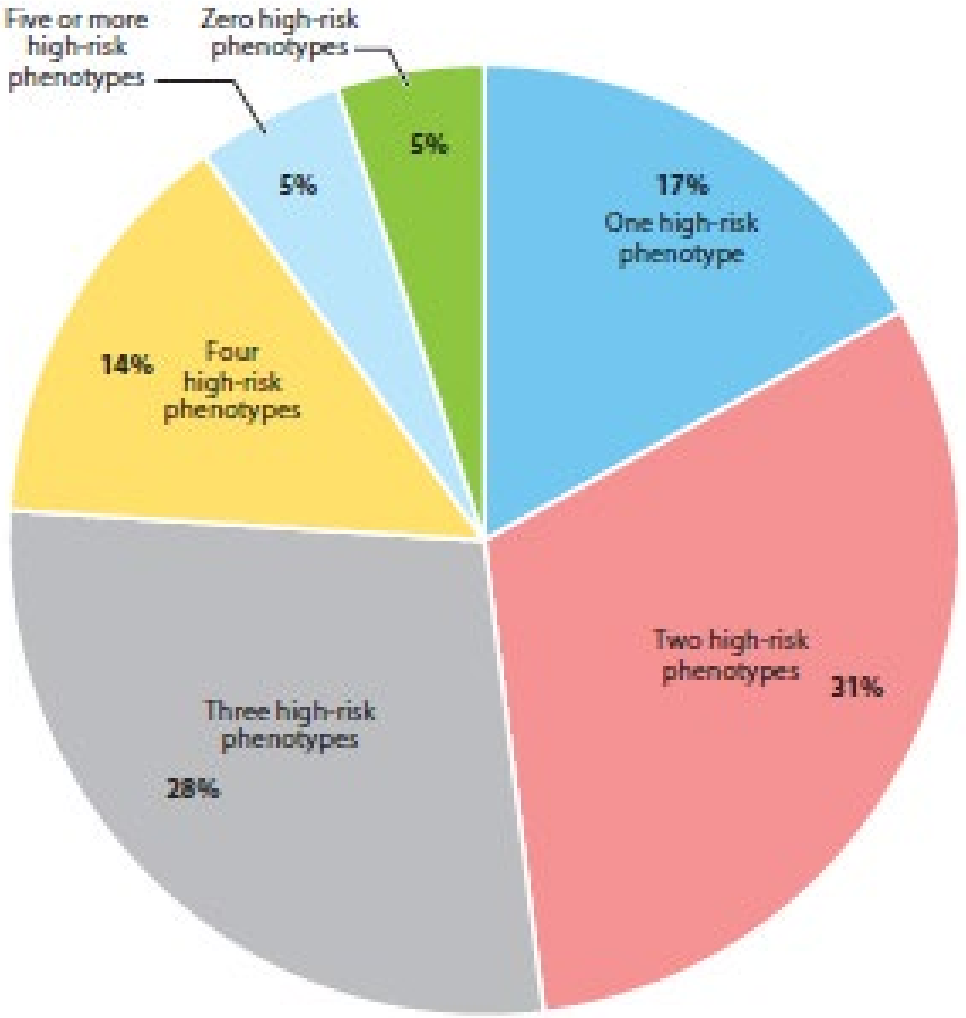
PG4KDS : Multiple steps to implement a new gene/drug pair

- Diplotype interpretation; clinical consults; problem list entries
- Build interruptive CDS (clinical decision support)
- Update formulary, drug policies as needed
- Update pt and clinician educational materials
- Build and complete competencies for clinicians
- Approval of Pharmacogenetics Oversight Committee
- Update public website; sharing with PGRN, PharmGKB, others

of patients who have received top 10 most prescribed PGx drugs at St. Jude (Q4-2019 to Q4-2020)

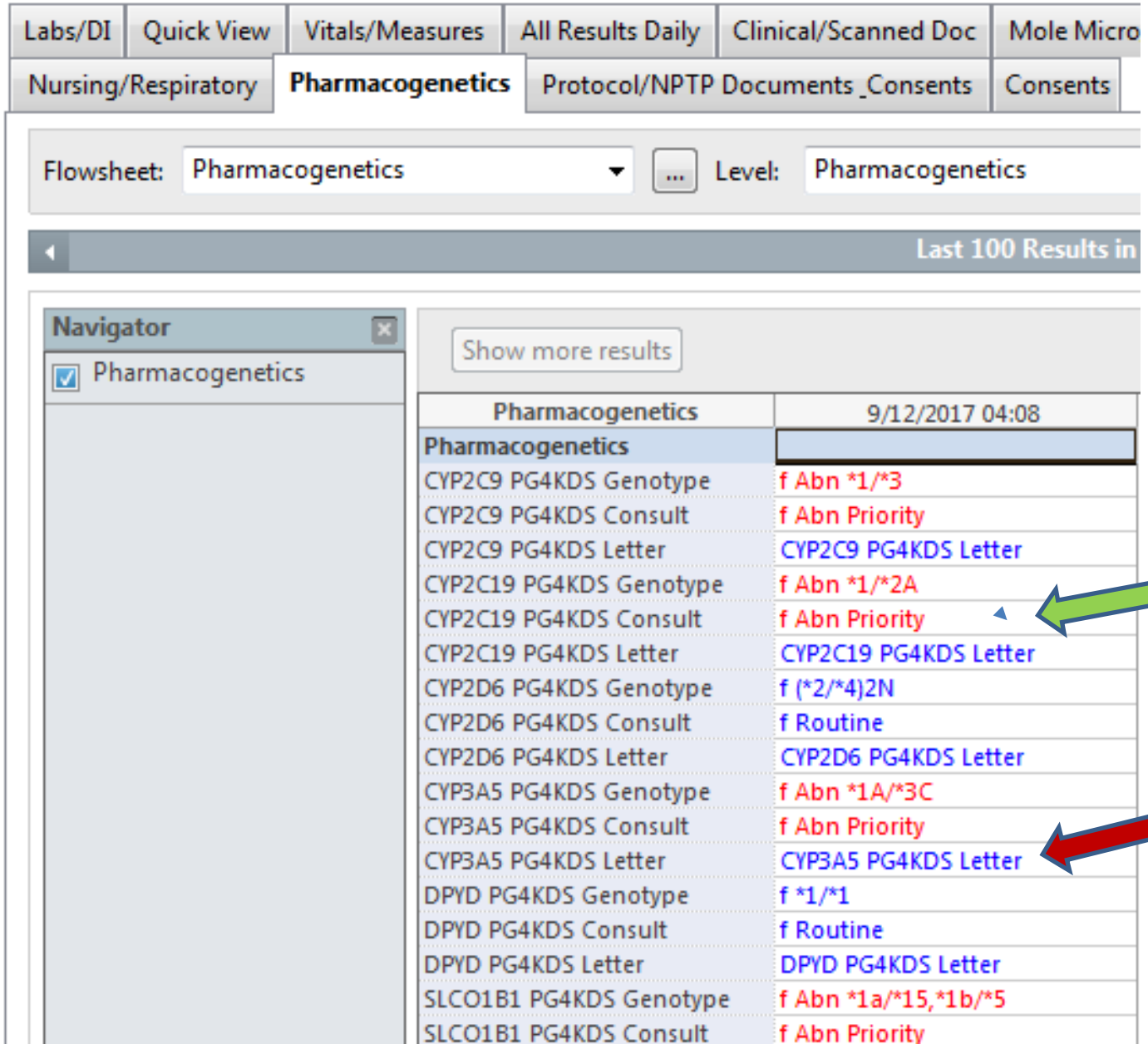


95% of St. Jude pts have at least one high-risk phenotype with first 14 genes



Haidar et al, 2022

Diplotypes entered on Pharmacogenetics Tab: not encounter-specific. Includes phenotypic tests.



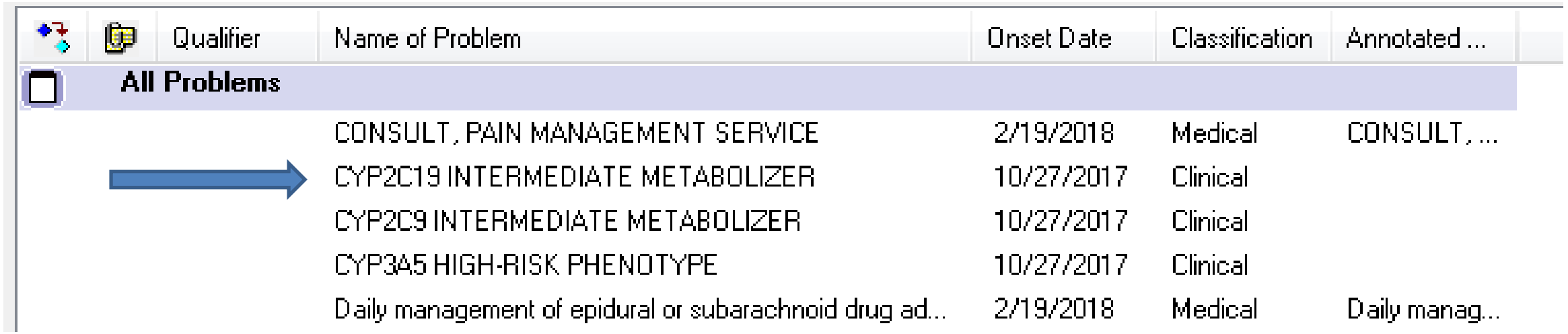
Epic: genomic indicators

Each test result has the diplotype and consult posted

Pt letter placed in EHR as well as pt portal

PG4KDS

High-risk diplotypes translated to phenotype, automatically populated into Problem List of EMR…but can also be entered manually



Qualifier	Name of Problem	Onset Date	Classification	Annotated ...
All Problems				
	CONSULT, PAIN MANAGEMENT SERVICE	2/19/2018	Medical	CONSULT, ...
	CYP2C19 INTERMEDIATE METABOLIZER	10/27/2017	Clinical	
	CYP2C9 INTERMEDIATE METABOLIZER	10/27/2017	Clinical	
	CYP3A5 HIGH-RISK PHENOTYPE	10/27/2017	Clinical	
	Daily management of epidural or subarachnoid drug ad...	2/19/2018	Medical	Daily manag...

Customized Decision support "behind the scenes":

Links high-risk diplotypes to ordering of applicable high-risk drug

Each high-risk result triggers medication reconciliation

PG4KDS

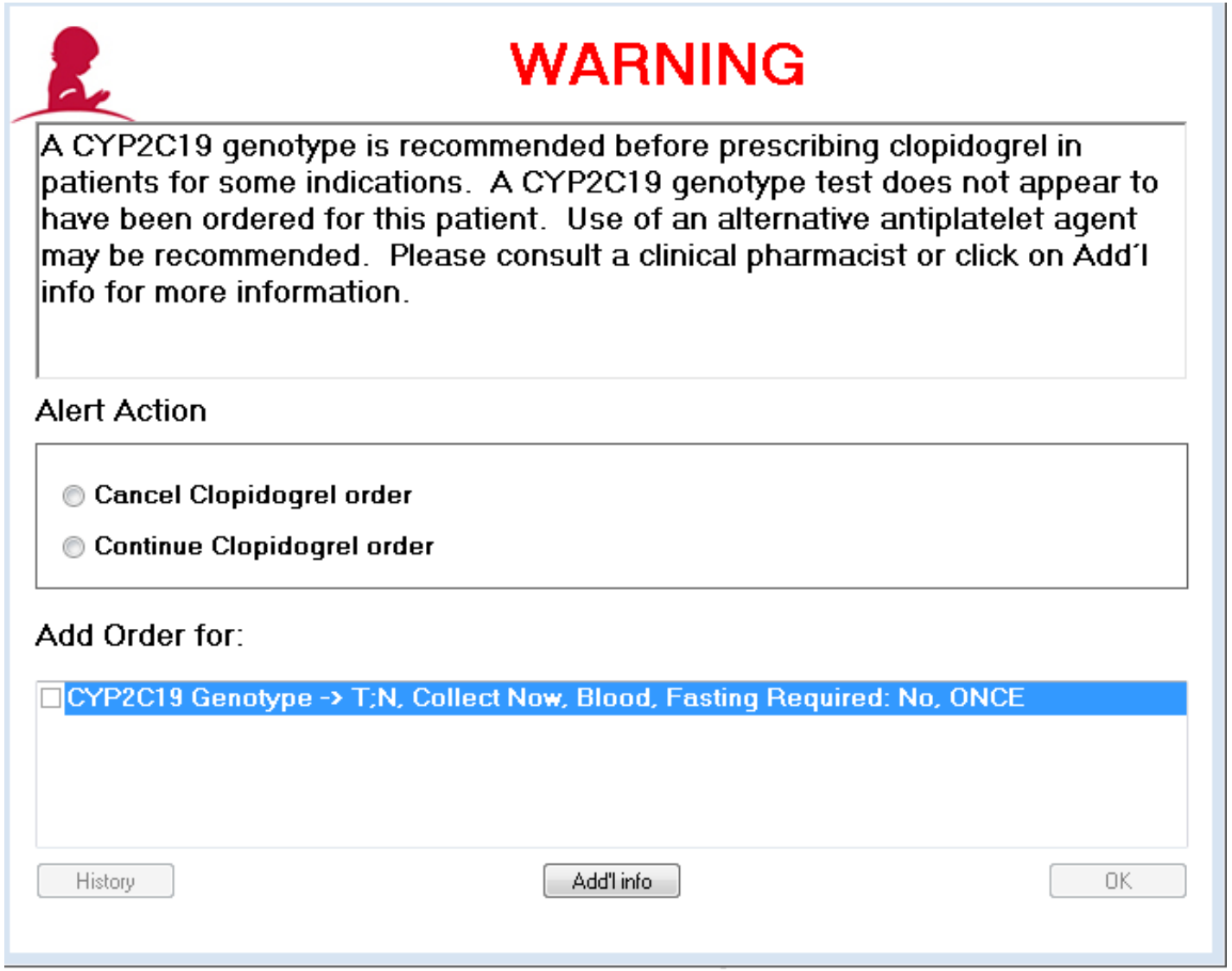
Interruptive alerts (active CDS) used to guide prescribing based on genetic test results

- Pre-test situation:
  - Check for genetic test and, if missing, guide prescriber to consider ordering the test
- Post-test situation:
  - Test result is high-risk and advice for prescribing alternatives should be presented
  - Test result is low-risk and no interruptive alert should be fired

PG4KDS

Pre-test Alerts Only for Select Gene/Drug Pairs---driven off the ABSENCE of a test result

- *CYP2C19* and clopidogrel
- *CYP2D6* and codeine, tramadol
- *DPYD* and fluoropyrimidines
- *TPMT/NUDT15* and thiopurines
- G6PD activity and rasburicase, methylene blue



Post-test alerts contain prescribing recommendations based on the PRESENCE of a high risk test result

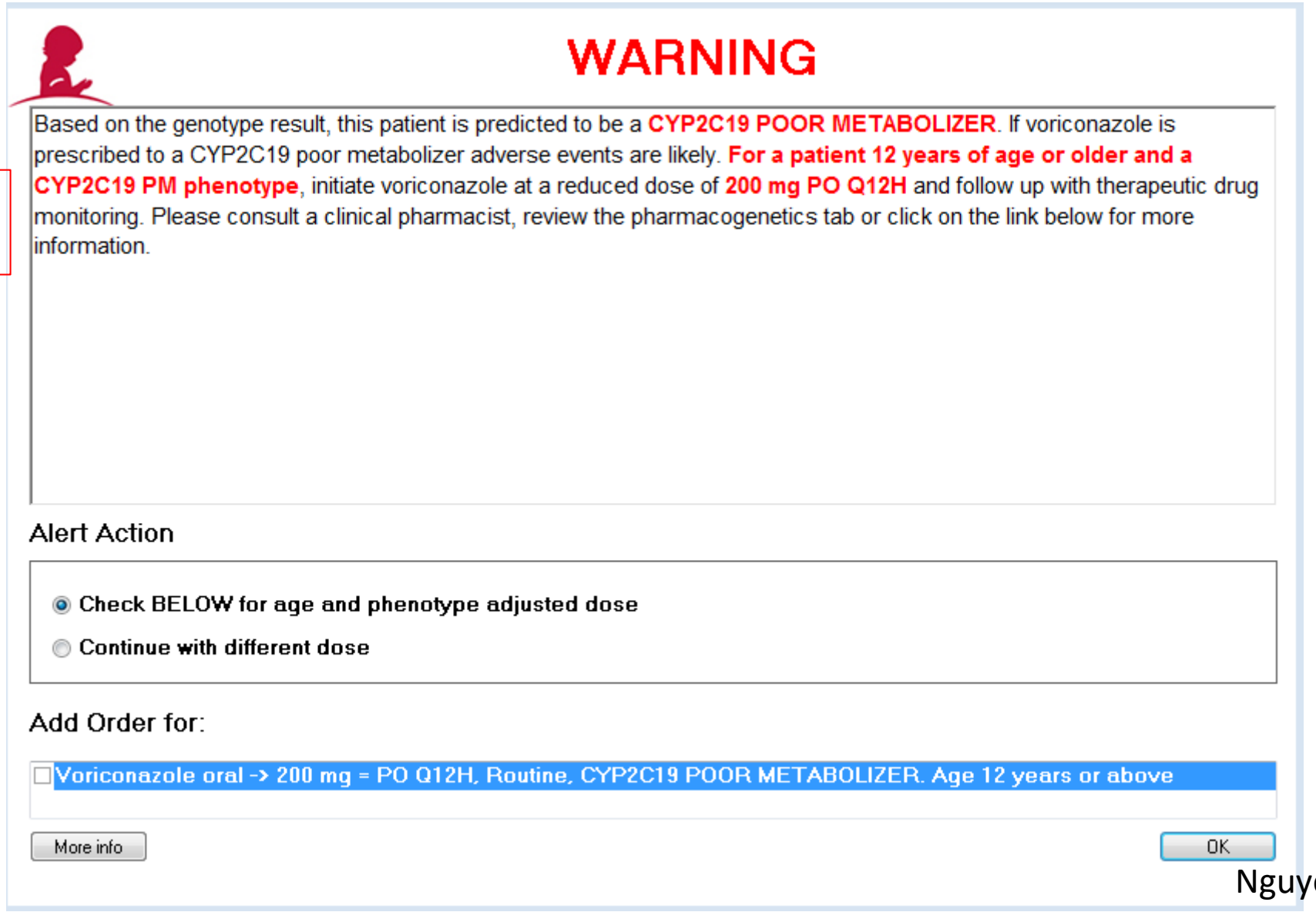
Drug: codeine
Gene: *CYP2D6*

PG4KDS

Nguyen et al *JAMIA* 2022

Post-test alert can incorporate non-genetic info too: based on *CYP2C19* phenotype, route of administration, age

Drug: voriconazole
Gene: *CYP2C19*

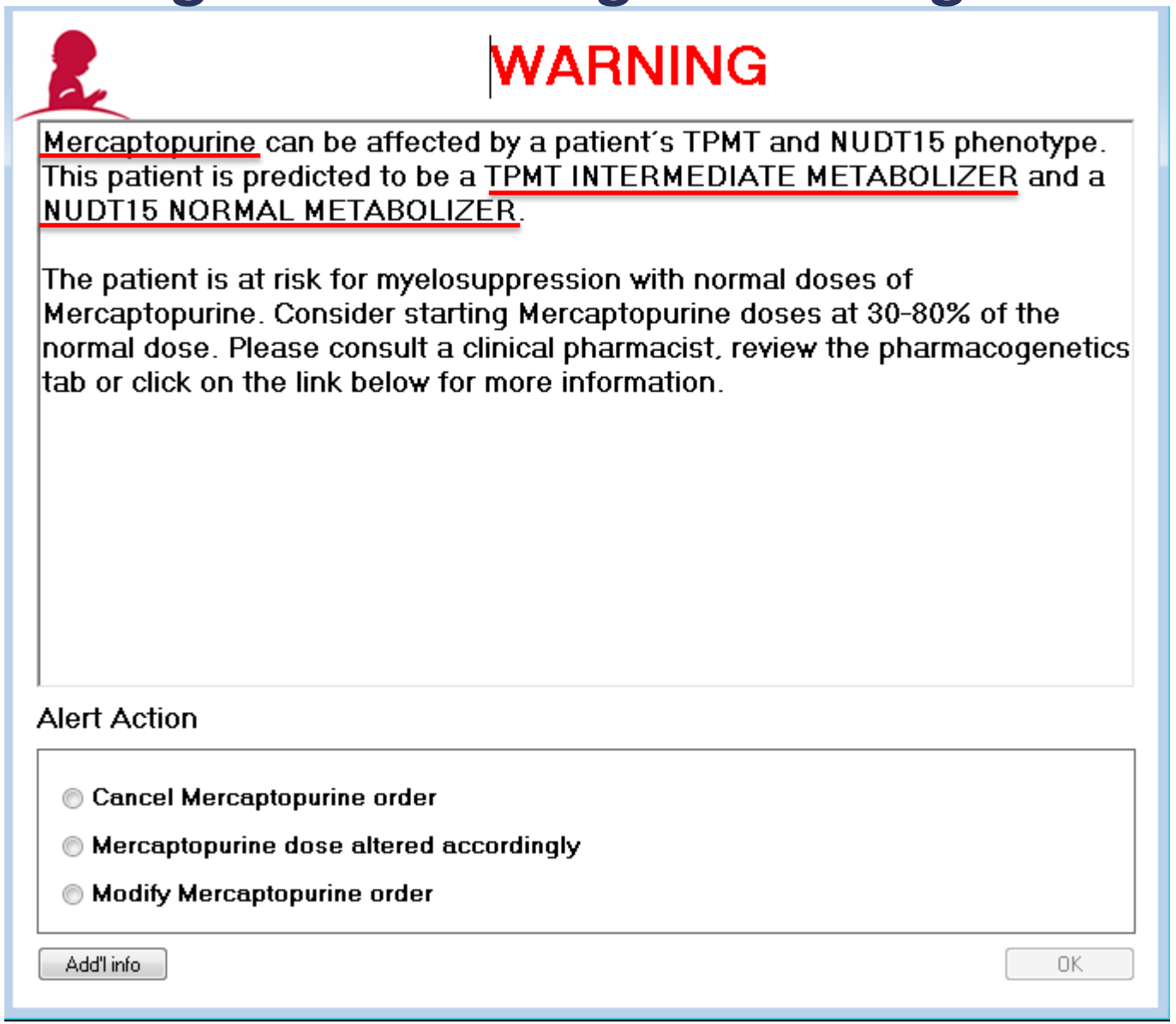


PG4KDS

Nguyen et al *JAMIA* 2022

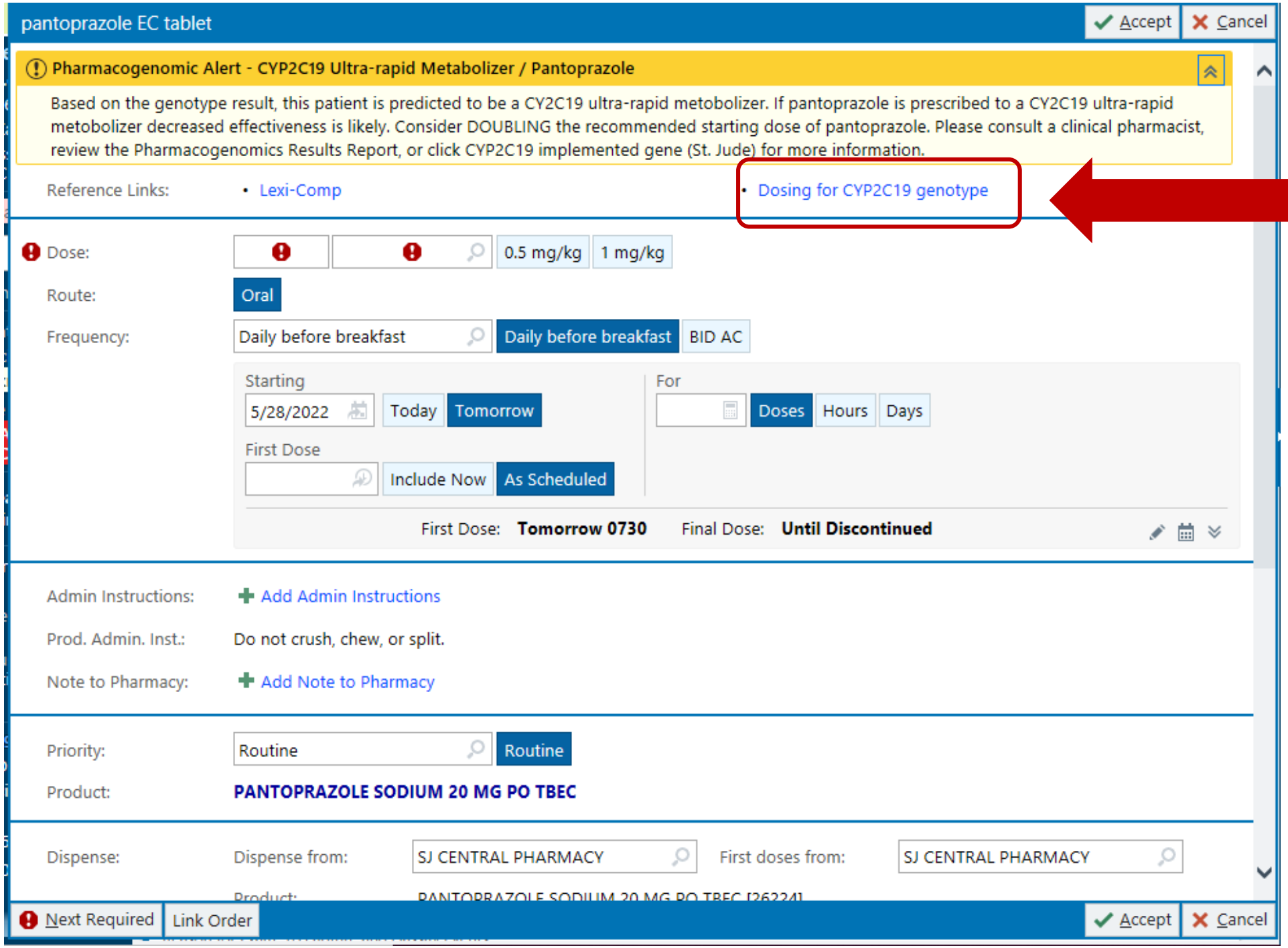
Post-test alert: based on 2 genes affecting same drug

Must create algorithms that work when one or both genes have results



PG4KDS

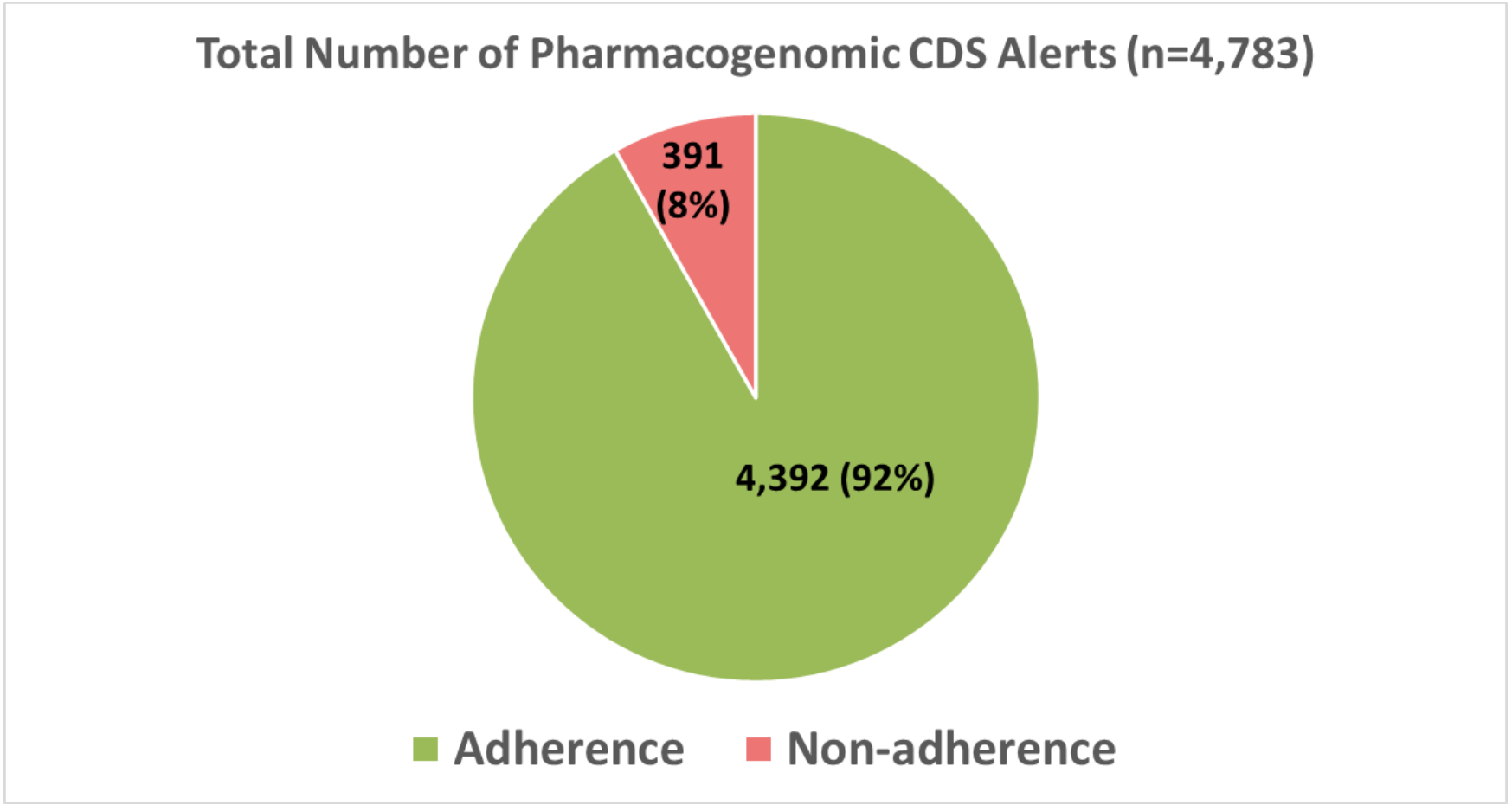
Nguyen et al *JAMIA* 2022



Epic BPAs

Links to our pharmacogenetic prescribing recommendation information

There has been high adherence by clinicians to the CDS alerts

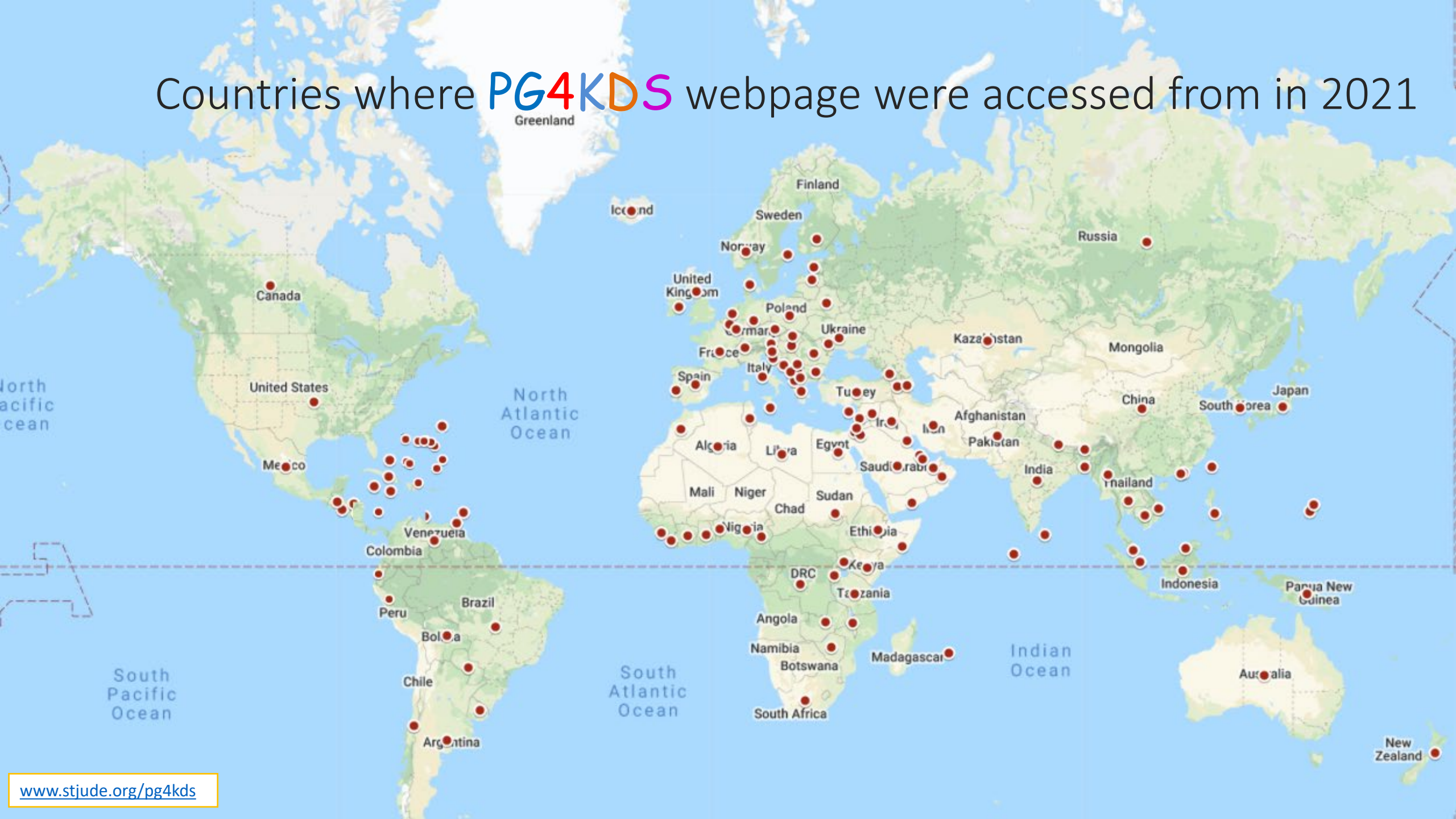


PG4KDS

May 2011 until November 2021. Adherence was defined as documentation that the CDS recommendations were followed (e.g., dose adjustment or selecting an alternative medication) or documentation of a clinically appropriate change in therapy

Nguyen et al *JAMIA* 2022

Countries where PG4KDS webpage were accessed from in 2021



www.stjude.org/pg4kds

St. Jude Children's Research Hospital

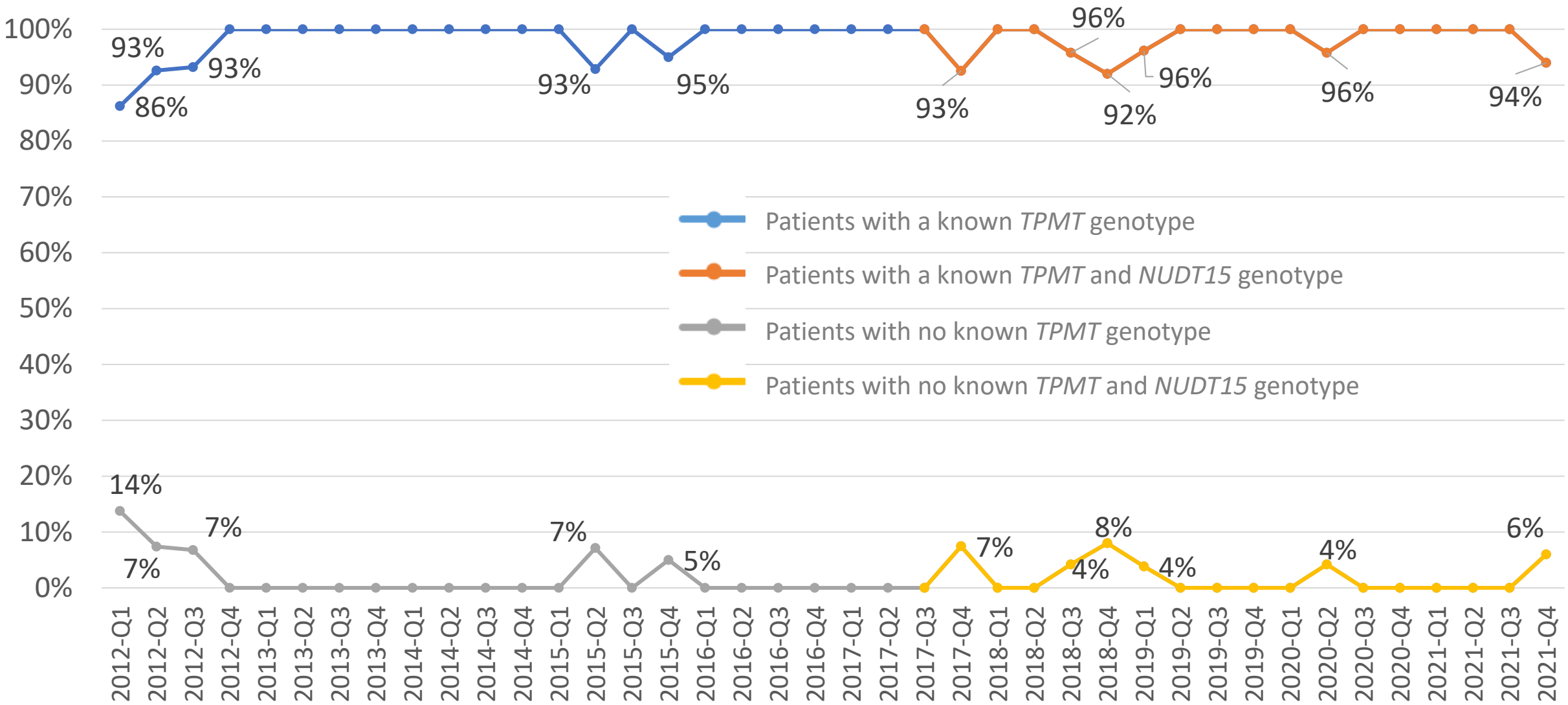
FY22-27 Strategic Plan

Goal 3

Reduce the toxicity of cancer therapy and enhance quality of life for all children who survive pediatric cancer

- Precision medicine expansion
  - Clinical genomics and pharmacogenomic services
  - Cancer Predisposition Clinic
  - Genomic translational research
- Proton therapy
- St. Jude LIFE and long-term effects of cancer immunotherapy and targeted therapy
- HPV Cancer Prevention Program

On dashboard for institutional patient safety metrics: % of thiopurine-naïve ALL patients who had a known *TPMT* and *NUDT15* genotype prior to initiating thiopurine therapy



** Patients with an unknown TPMT or NUDT15 genotype who initiated thiopurine therapy after an allogeneic HSCT were excluded from this reporting*

PG4KDS interesting cases

- Patient with persistent GI bleed unresponsive to pantoprazole, found to be a *CYP2C19* ultra-rapid metabolizer and was on inadequate dose
- Patient routinely taking codeine prior to being accepted to St. Jude. Codeine made her fall asleep, mother thought it was normal. Found to be a *CYP2D6* ultra-rapid metabolizer
- *CYP2C19* genotype ordered on a patient about to start on clopidogrel. Found to be a *CYP2C19* poor metabolizer. Alternative therapy initiated

PG4KDS and St. Jude Acknowledgements

PI: Cyrine Haidar

Clinical Pharmacy Specialists: Shane Cross, John McCormick, Jen Pauley, Hope Swanson, PJ Barker, Diana Wu, Andy Christensen, Melissa Bourque, Allison Bragg, Deb Ward, Joe Sciasi, Deni Trone, Tim Jacobs

Don Baker & Clinical Informatics

Pathology: Charles Mullighan, Larissa Furtado

Physician Investigators: Aditya Gaur, Jane Hankins, Ulrike Reiss, Amar Gajjar, Alberto Pappo, Melissa Hudson, Ching-Hon Pui, Sima Jeha, Kim Nichols, Paulina Velasquez, Andy Davidoff, Raja Khan, Seth Karol, Kavitha Raghavan

RNs: Sheri Ring, Lisa Walters, Paula Condy, Terri Kuehner, Margaret Edwards

Computing: Nancy Kornegay, Wenjian Yang, Carl Panetta, Ben McKinley

Pharmaceutical Sciences:

William E. Evans, Jun Yang,

Alejandro Molinelli, Bill Greene

Kristine Crews, James Hoffman

PG residents: Kevin Hicks, Gillian Bell, Mark Dunnenberger, Rose Gammal, Amy Pasternak, Jennifer Hockings, Cameron Thomas, Keito Hoshitsuki, Sarah Morris, Jenny Nguyen

Genetic Counselors

Family Advisory Committee

Biostatistics: Cheng Cheng, Deqing Pei

Ulrich Broeckel, M.D.

Rachel Lorier

Amy Turner

CPIC™
Clinical Pharmacogenetics Implementation Consortium

Team

CPIC Co-Principal Investigators
Kelly E. Caudle, Pharm.D., Ph.D.
St. Jude Children's Research Hospital

Teri E. Klein, Ph.D.
Stanford University

Co-Investigator
Mary V. Relling, Pharm.D.
St. Jude Children's Research Hospital

CPIC Informatics Co-Directors
Michelle Whirl-Carrillo, Ph.D.
Stanford University

James M. Hoffman, Pharm.D.
St. Jude Children's Research Hospital

Stanford CPIC Coordinator
Michelle Whirl-Carrillo, Ph.D.
Stanford University

Steering Committee

Teri E. Klein, Ph.D.
Stanford University

Kelly E. Caudle, Pharm.D., Ph.D.
St. Jude Children's Research Hospital

Michelle Whirl-Carrillo, Ph.D.
Stanford University

Mary V. Relling, Pharm.D.
St. Jude Children's Research Hospital

Dan M. Roden, M.D.
Vanderbilt University

Rachel F. Tyndale, Ph.D.
University of Toronto and CAMH

Larissa Cavallari, Pharm.D.
University of Florida

Stuart Scott, Ph.D.
Icahn School of Medicine at Mount Sinai

Sara Van Driest, M.D., Ph.D.
Vanderbilt University

Scientific Advisory Board

Julie A. Johnson, Pharm.D.
University of Florida

Gwendolyn A. McMillin, Ph.D.
ARUP Laboratories

Robert Nussbaum, M.D.
University of California, San Francisco

Heidi Rehm, Ph.D.
Partners Healthcare

Marc S. Williams, M.D.
Geisinger

Sandy Aronson
Partners Personalized Medicine

Justin B. Starren, M.D., Ph.D.
Northwestern University

- And:
- CPIC informatics
- Andrea Gaedigk
- Other CPIC staff and collaborators: Rose Gammal, Pharm.D.; Sarah Morris, Pharm.D.; Katrin Sangkuhl, Ph.D.; Li Gong, Ph.D.; Rachel Huddart, Ph.D.; Ryan Whaley

NIH National Institutes of Health

This work was funded by the National Institutes of Health (NIH) (R24GM115264 and U24HG010135)