All 4 slides decks from this session are contained in this file in alphabetical order by speaker last name.

Please text your attendance (within 24 hours) then complete the post-test and evaluation (within 4 weeks) at https://stjude.cloud-cme.com/COG or contact cpe@stjude.org with questions.

CHILDREN'S ONCOLOGY GROUP

The Betsy Poon Pharmacy Education Series

2025 COG Spring Meeting

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Assessment of *TPMT/NUDT15* Pharmacogenomic Implementation for Thiopurine Dosing in Children with Cancer

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St. Jude Children's Research Hospital, Memphis, TN

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Conflicts of Interest/Disclosures

There are no relevant financial interests in the last 24 months to disclose for any person with control over the content of this presentation

All relevant financial relationships listed for the individual have been mitigated by the ACPE accredited provider (St. Jude Continuing Pharmacy Education Program).

Abbreviations

- PGx-Pharmacogenomics
- ALL- Acute Lymphoblastic Leukemia
- EHR-Electronic Health Record
- CDS-Clinical Decision Support
- NCCN-National Comprehensive Cancer Network
- COG-Children’s Oncology Group
- IRB-Institutional Review Board

Learning Objectives

- Describe the implementation strategies for a successful implementation of pharmacogenetics (PGx) testing.
- Describe the barriers to a successful implementation of PGx testing.
- Understand the importance of the use of the electronic health record (EHR) for PGx testing.

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Off-label Use Disclosure: This session does not include a discussion of off-label treatment and investigational agents not approved by the FDA for use in the US.

Does your institution genotype patients for *TPMT*, *NUDT15* or both prior to use of thiopurines?

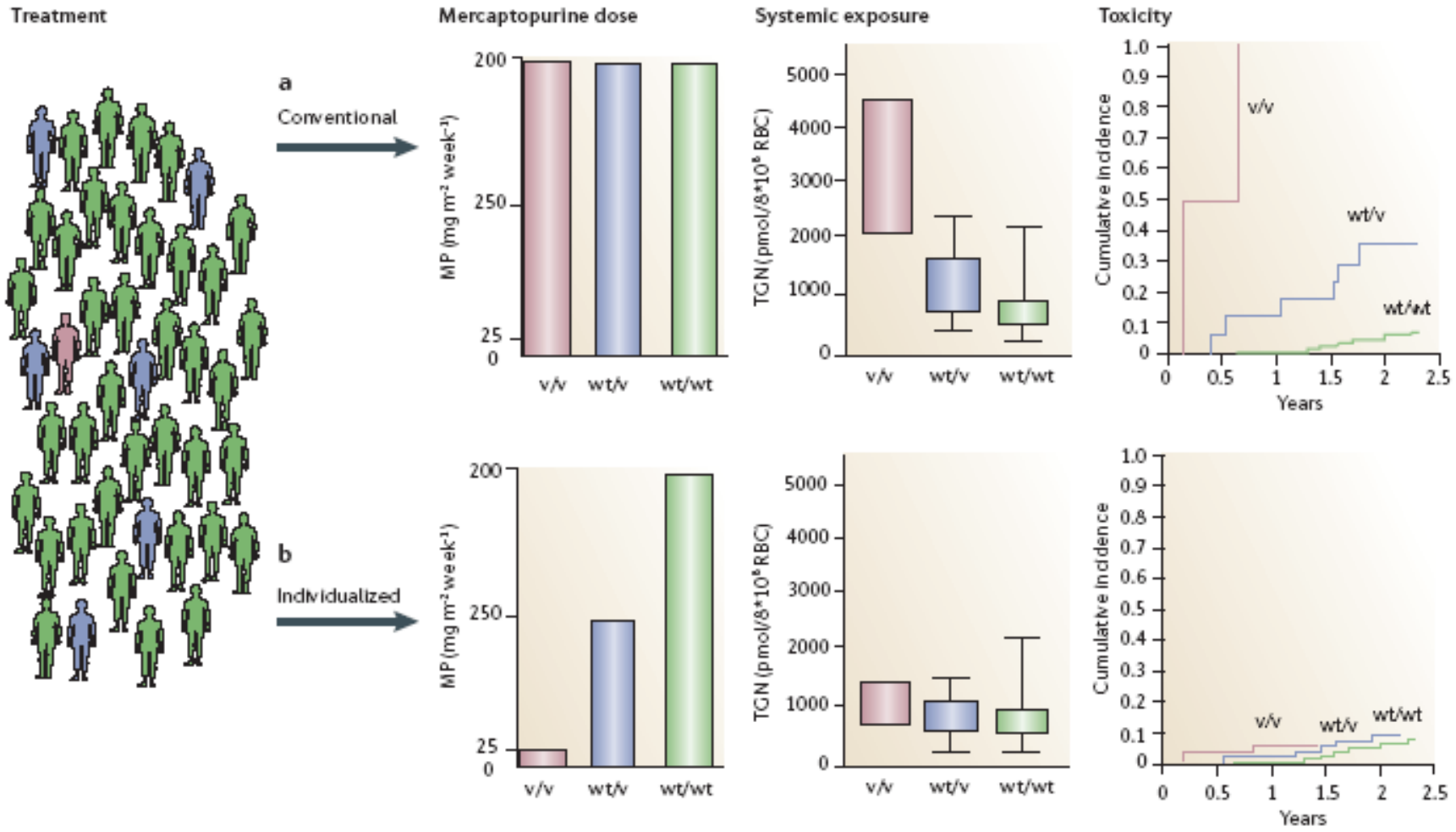
A. *TPMT*

B. *NUDT15*

C. *TPMT* and *NUDT15*

D. No

6MP dosing WITH pharmacogenomics reduces toxicity in pediatric patients with ALL



Cheok, MH and Evans WE. *Nat Rev Cancer*. 2006; 6(2): 117-29.

Testing recommended in guidelines/protocols

- NCCN Guidelines Version 2.2025 for Pediatric ALL
  - Genetic testing for no function alleles of *TPMT* and NUDT15 should be considered prior to the initiation of thiopurine therapy, or if excessive toxicity is encountered following treatment with thiopurines.
  - For patients who are normal metabolizers of *TPMT* or *NUDT15* who do not appear to tolerate thiopurines, consider measuring erythrocyte thiopurine metabolites and/or erythrocyte TPMT activity. Genetic testing may not identify rare or previously undiscovered no function alleles.
  - Utilizes CPIC recommendations
- COG protocols
  - Example AALL1732
  - *TPMT* and *NUDT15* genotype (*TPMT* highly recommended for all subjects; *NUDT15* is highly recommended for subjects of Hispanic/Native American or East Asian ancestry, and optional for all other subjects).

CPIC provides PGx clinical practice guidelines

- >750 members (clinicians and scientists)
- 28 guidelines (and counting!)
- >520 institutions
- 34 genes
- 49 countries
- >160 drugs
- >50 CPIC informatics from >40 organizations
- 14 Observers (NIH, FDA, professional societies)

Cpicpgx.org

Updated August 2024

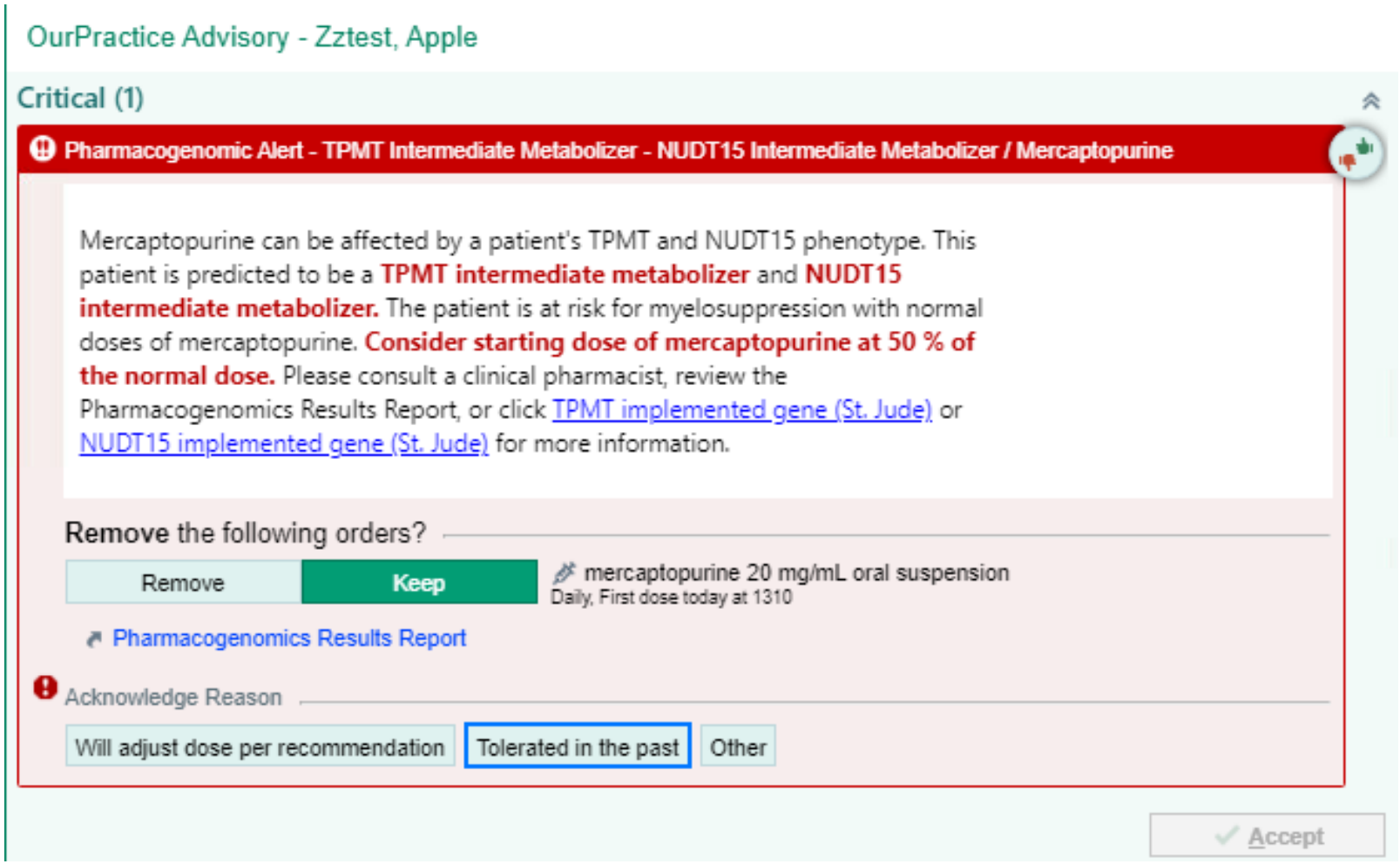
Common features of successful PGx implementation

- Stakeholder engagement including champions
- Laboratory and test selection
- Cost/reimbursement
- EHR integration
- Return of results to patients/families

Integration of PGx results in EHR is critical

- At a leading pediatric hospital where they used one system for reporting with another for the EHR
- Accessing PGx results took 6 clicks and multiple browser windows to get the results
- Serious safety event occurred where an ALL patient received the usual dose of mercaptopurine and had severe infection/myelosuppression and nearly died
- Patient was a TPMT poor metabolizer, and the results were in the chart when the first dose was given

St. Jude Children's Research Hospital



- PGx Program led by Cyrine Haidar, PharmD
- Pre-emptively genotyped nearly 8,000 patients to date for 16 genes and 75 drugs
- Result available in the EHR prior to thiopurine prior to administration.
- Results entered as discrete field (not time stamped)
- Multidisciplinary team

Study aim

- This study aimed to assess implementation strategies, priorities, challenges, and lessons learned across COG institutions who have or have not implemented *TPMT* and/or *NUDT15* pharmacogenomic testing to guide thiopurine dosing in children with Acute Lymphoblastic Leukemia (ALL).

Methods

- An online survey utilizing Qualtrics® was distributed via the COG pharmacist's listserv reaching 227 COG institutions.
- The survey included dichotomous, multiple-choice, and ranking questions as well as open-ended prompts to gather data regarding *TPMT* and/or *NUDT15* pharmacogenomic testing at COG institutions.
- Survey participation was voluntary. The study was reviewed by the St. Jude Children's Research Hospital IRB and determined to be exempt.

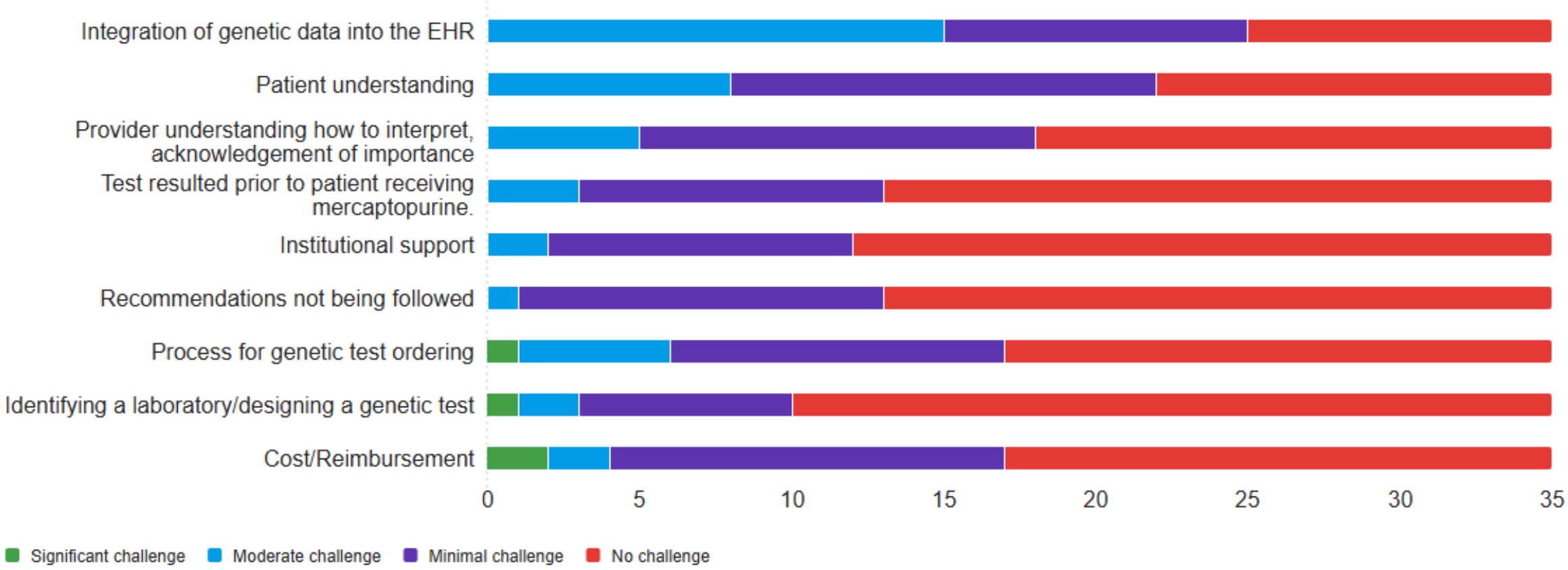
Results

- To date, pharmacists from 42 COG institutions completed the survey.
- 85% of responding hospitals were based in a large, academic setting.

- *TPMT*
  - 98% testing:
    - 95% in all patients
    - 5% reactively
    - 54% prior to consolidation
    - 30% prior to remission induction

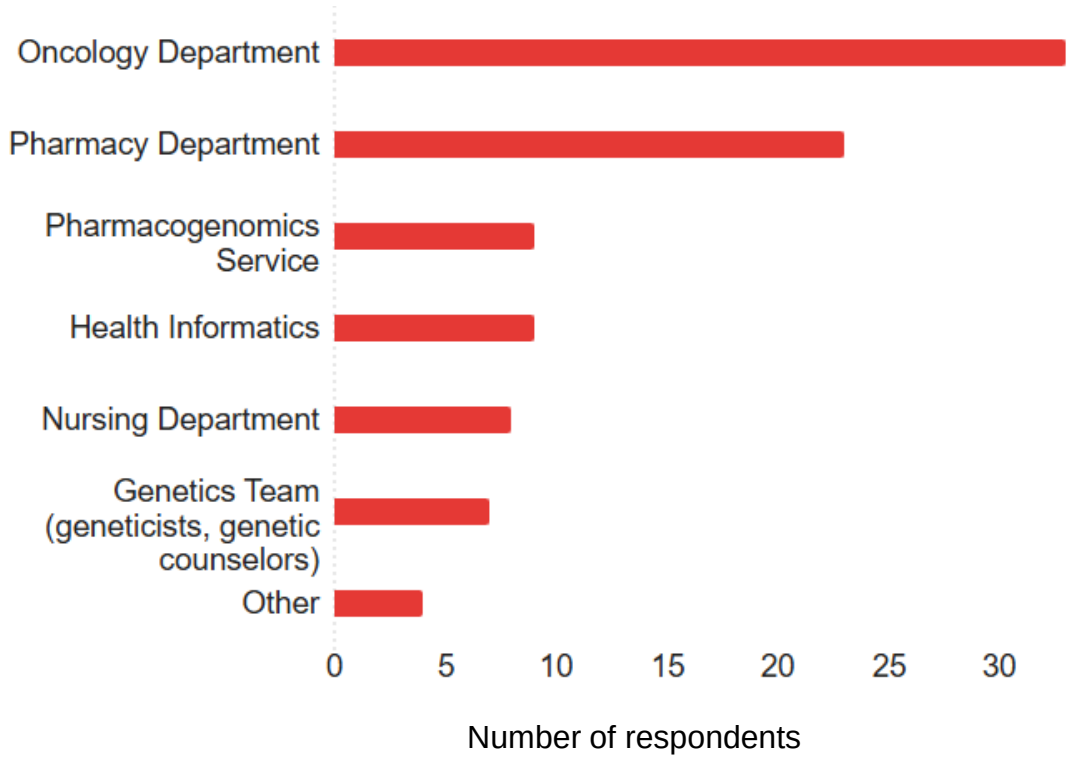
- *NUDT15*
  - 95% testing
    - 84% in all patients
    - 3% reactively
    - 8% only in Hispanic/Native American or East Asian ancestry
    - 46% prior to consolidation
    - 84% prior to remission induction

Challenges to implementation/testing

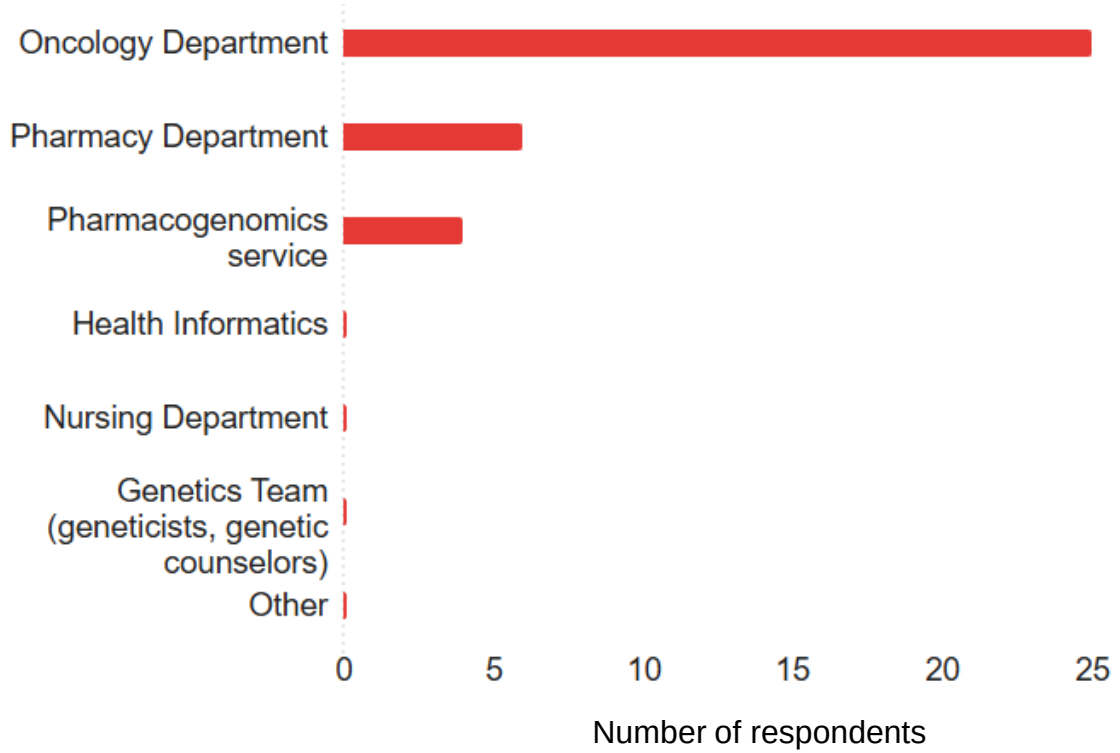


Stakeholder engagement

Who is involved (select all)?



Who leads/champions?



Lab/test selection and reimbursement

- Where is the test performed*
  - 37% (n=15) In-house
  - 41% (n=17) Send out to another institution
  - 48% (n=19) Commercial lab
- Type of test*
  - 29% (n=12) Single gene test *TPMT* alone and/or *NUDT15*
  - 67% (n=27) *TPMT/NUDT15* only panel
  - 34% (n=14) Multi-gene test/panel which includes *TPMT* and/or *NUDT15*

*Reported on a 5-point Likert scale; reporting “always” and “most of the time”

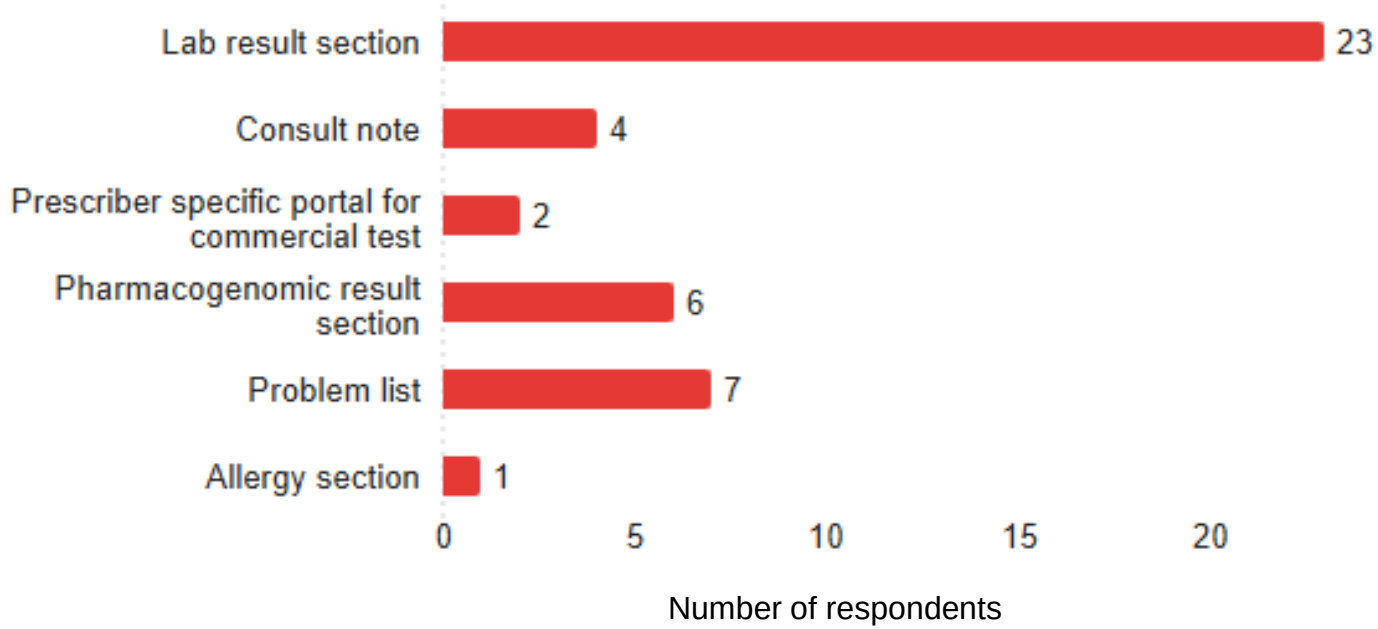
Lab/test selection and reimbursement

- Turnaround time
  - Median 5-8 days
- Reimbursement/payment*
  - 80% Insurance/3rd party
  - 0% Patient (5 respondents sometimes)
  - Some indicating it is bundled

*Reported on a 5-point Likert scale; reporting “always” and “most of the time”

EHR integration

- 93% reported results are integrated into the EHR
  - 15 (35%) reported scanned pdfs or not integrated into a discrete field



EHR integration

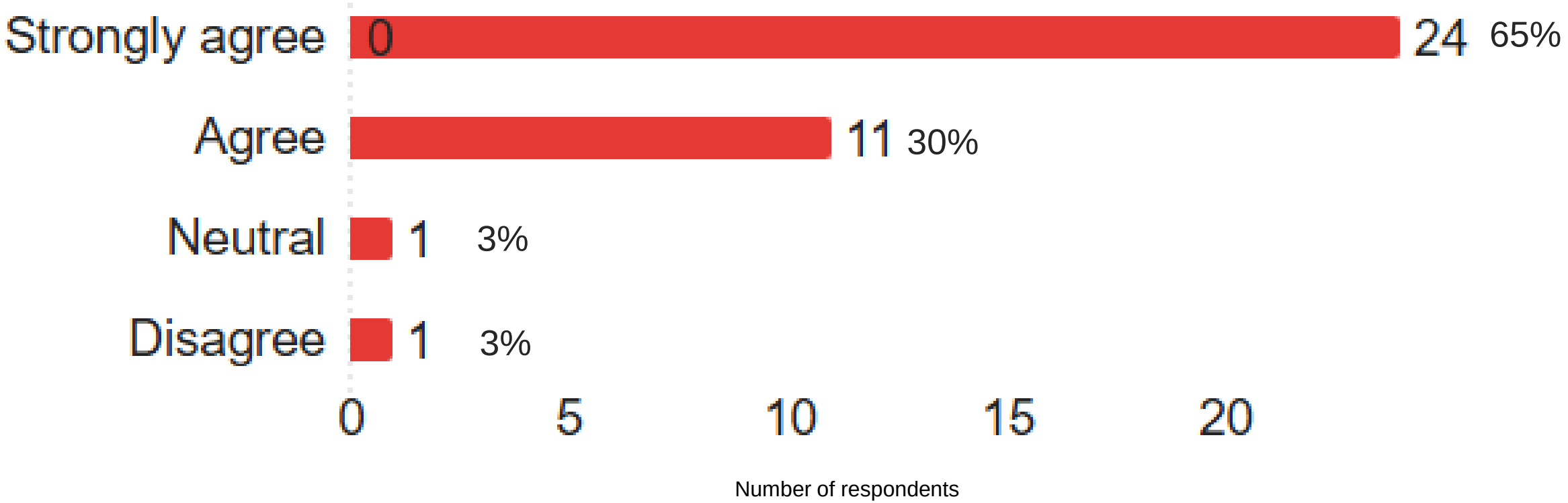
- Pre-test alerts
  - 81% (n=33) do NOT provide pre-test interruptive alerts
    - 52% (n=17) pre-selected in order set
    - 10% (n=3) in order set but not pre-selected
    - 32% (n=13) do not provide either
- Post-test alerts
  - 74% (n=30) do NOT provide post-test alerts
  - Of the 26% (n=11) providing CDS:
    - 45% (n=5) interruptive
    - 18% (n=2) in-line alerts
    - 36% (n=4) alert in drug ordering window

Return of results to patients/families

- Who returns the result to the patient?
  - 86% oncologists
  - 9% Pharmacists
  - 9% PGx service
  - 0% Genetic counselors
  - 28% patient portal (no provider involved)
  - 13% do not return results to the patient

*Reported on a 5-point Likert scale; reporting “always” and “most of the time”

Has your implementation/testing been successful?

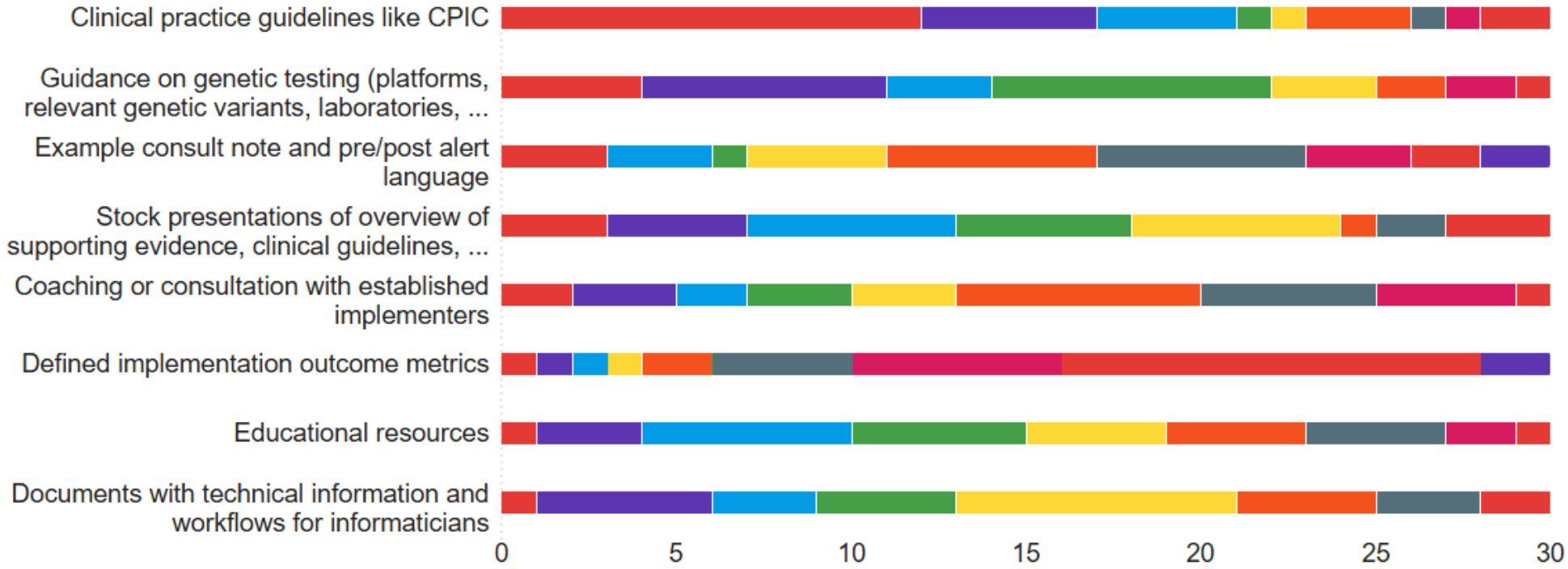


Conclusions

- Many COG institutions have implemented PGx for thiopurine use but many have not integrated these results into the EHR as discrete data.
- Still collecting data!!
- Need more institutions from community and/or resource limited hospitals to take the survey
- Need more institutions not testing to take the survey
- Once the study is complete, we will be developing and sharing resources to support implementation efforts

Conclusions

- Resources that would have been or were beneficial to enhance implementation?



Please take the survey!!!

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Acknowledgements

- Contributors:
  - Cyrine Haidar, PharmD
  - Melissa Bourque, PharmD
  - Brooke Bernhardt, PharmD
  - Kris Crews, PharmD
  - David Stenehjem, PharmD
  - James Hoffman, MS, PharmD

Question & Answer Session

Kelly E. Caudle, PharmD, PhD, BCPS, FCCP

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The Betsy Poon Pharmacy Education Series

2025 COG Spring Meeting

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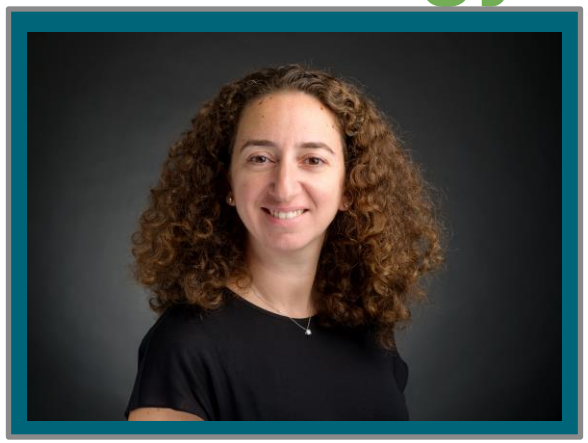
Empowering Patients: Establishing a Pharmacist-Led Pharmacogenomics Clinic in Pediatric Oncology



Cyrine-Eliana Haidar, Pharm.D, BCPS, BCOP, FASHP

Associate Member

St. Jude Children's Research Hospital

Memphis, TN

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Conflicts of Interest/Disclosures

NAME	COMPANY	RELATIONSHIP
Cyrine Haidar, Pharm.D.	Nothing to disclose	

All relevant financial relationships listed for the individual have been mitigated by the ACPE accredited provider (St. Jude Continuing Pharmacy Education Program).

Learning Objectives

- Evaluate the utility of implementing a pharmacogenomics clinic in a pediatric oncology setting

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History of Pharmacogenomic Testing at St. Jude

- Single gene testing for select patients started with *TPMT* (1991) → *UGT1A1* (2006) → *CYP2D6* (2007)
- Initial steps to implement a Clinical Pharmacogenomics Service started in 2005
- Institution-wide preemptive array pharmacogenomic testing started in 2011 through the PG4KDS protocol
  - Test results used daily to guide pharmacotherapy

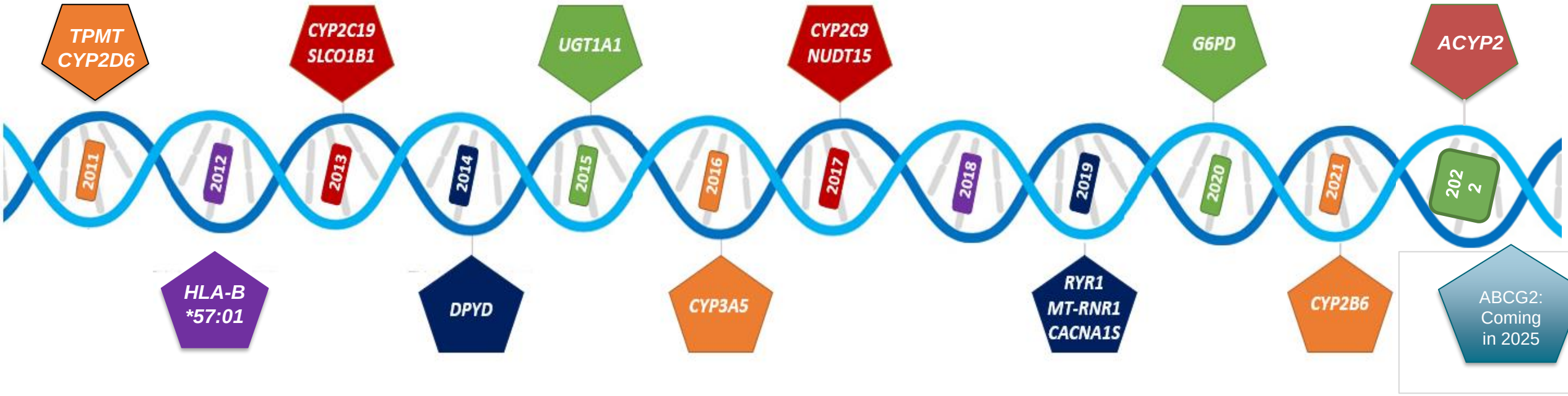
Crews KR. *Am J Health Syst Pharm.* 2011;68(2):143-150.

PG4KDS: The Process

1. Patient consent
2. Blood sample
3. Genotyping (1191 genes)
4. Results Released in EHR (16 genes)
5. Clinical Decision Support
6. Return of Results Prescribers & Patients

Haidar CE. *Annu Rev Genomics Hum Genet*. 2022;23:449-473.

16 Gene Test Results Are Returned in the Medical Record and Used Daily to Adjust Medication Therapy



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Haidar CE. *Annu Rev Genomics Hum Genet*. 2022;23:449-473.

16 Genes and 75 Drugs Implemented

- ***HLA-B*57:01*** *(1%)*
  - Abacavir-2012
- ***CYP2D6*** *(17%)*
  - Codeine-2011
  - Tramadol-2012
  - Oxycodone-2013
  - Amitriptyline, nortripyline-2014
  - Clomipramine, imipramine, trimipramine, doxepin-2016
  - Fluoxetine, paroxetine-2012
  - Ondansetron-2013
- ***CYP2C19*** *(62%)*
  - Clopidogrel-2103
  - Amitriptyline-2014
  - Clomipramine, imipramine, trimipramine, doxepin-2016
  - Voriconazole-2015
  - Omeprazole, pantoprazole, lansoprazole-2018
  - Citalopram, escitalopram, sertraline-2022
- ***CACNA1S/RYR1*** *(0.3%)*
  - Enflurane, methoxyflurane, desflurane, halothane, isoflurane, sevoflurane-2019
  - Succinylcholine-2019
- ***CYP3A5*** *(41%)*
  - Tacrolimus-2015
- ***ACYP2*** *(8%)*
  - Cisplatin-2022
- ***CYP2B6*** *(5%)*
  - Methadone-2021
  - Efavirenz-2021
- ***SLCO1B1*** *(13%)*
  - Simvastatin -2013
- ***TPMT/NUDT15*** *(11%)*
  - Mercaptopurine, thioguanine-2011/2017
  - Azathioprine -2011/2017
- ***DPYD*** *(0.4%)*
  - Fluorouracil, capecitabine-2014
- ***UGT1A1*** *(28%)*
  - Atazanavir-2015
- ***CYP2C9*** *(32%)*
  - Celecoxib-2017
  - Meloxicam, ibuprofen-2020
- ***MT-RNR1*** *(0.2%)*
  - Amikacin, gentamicin, tobramycin-2019
- ***G6PD*** *(2%)*
  - Dapsone, methylene blue, nitrofurantoin, phenazopyridine, primaquine, rasburicase-2020
  - Toluidine blue, pegloticase, tafenoquine-2022

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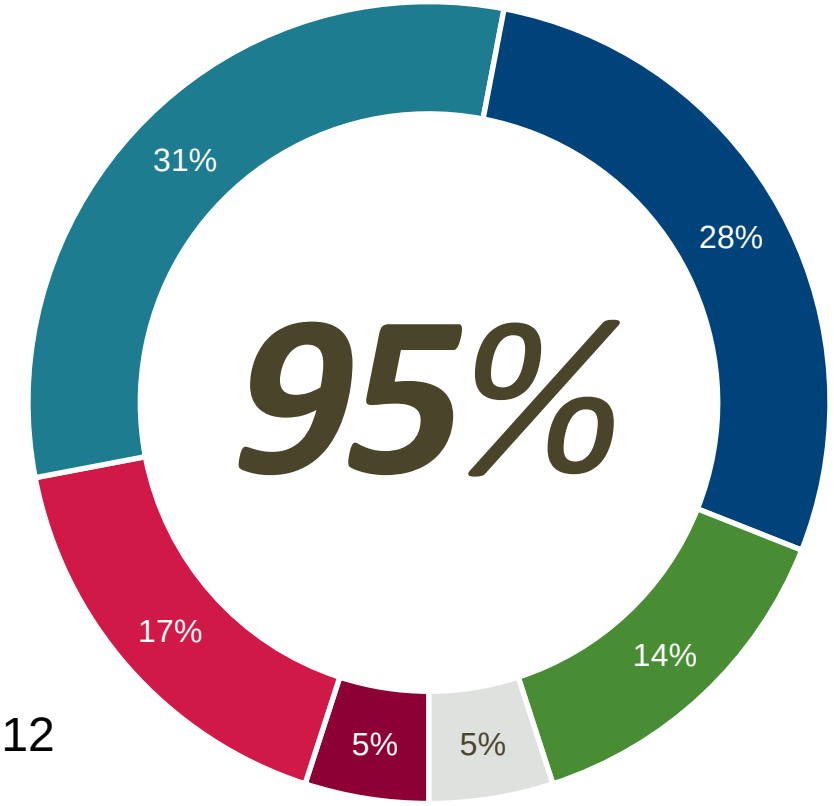
Percentage in parenthesis denotes % of patients enrolled on PG4KDS protocol who have a high-risk phenotype for the gene

www.stjude.org/pg4kds

Frequency of Actionable Pharmacogenomic Test Results



n=5,912

of patients genotyped on the had at least one high-risk pharmacogenomic in their health record

- Zero high-risk results
- 1 high-risk result
- 2 high-risk results
- 3 high-risk results
- 4 high-risk results
- 5 or more high-risk results

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Haidar CE. *Annu Rev Genomics Hum Genet*. 2022;23:449-473.

Establishing a Pharmacogenomics Clinic

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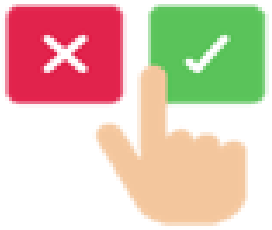
Pharmacogenomics Clinic Process

Pharmacogenomic Results in EHR

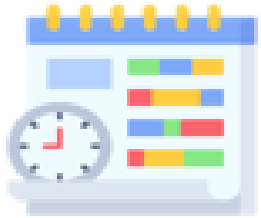


Review for Clinic Eligibility

Patients

Parents

External Referral



Schedule Visit

Clinicians

Patient Counseling by Pharmacist

Genetic Counselor Visit

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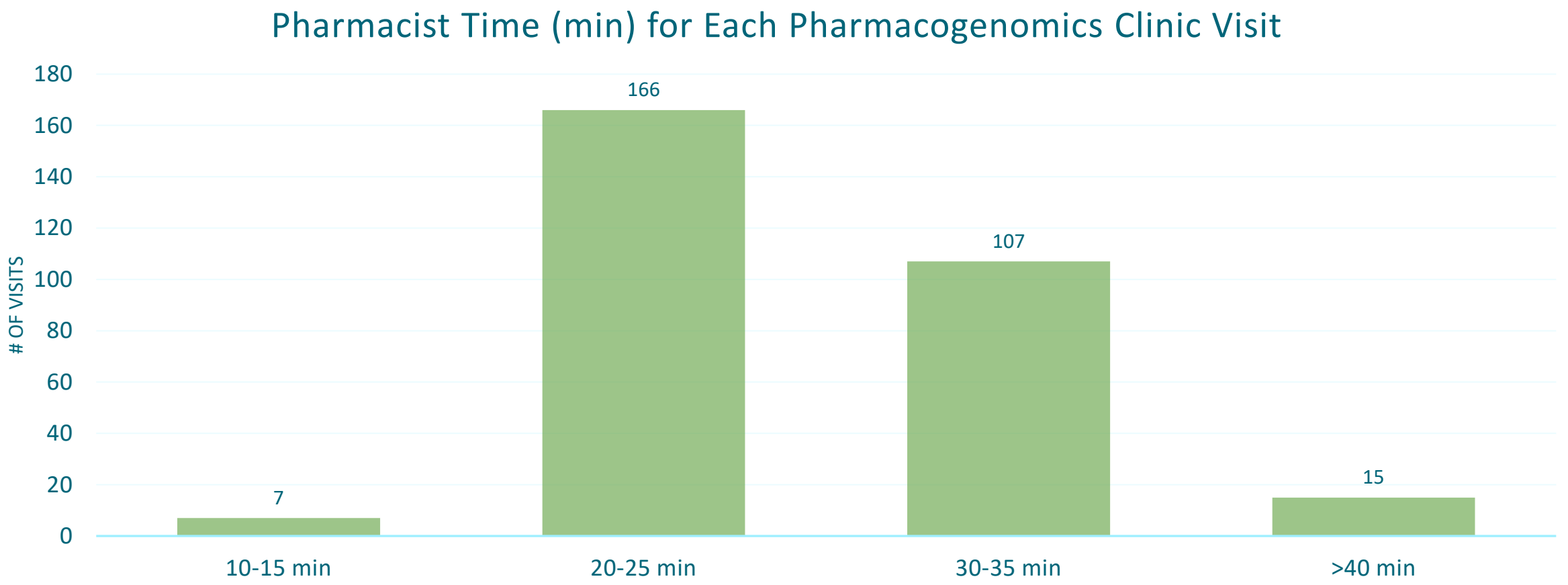
Haidar CE. *Annu Rev Genomics Hum Genet*. 2022;23:449-473.

Pharmacogenomics Clinic Established in November 2023

Patient Demographics and Characteristics (n=295)			
Age, years (median, range)	9.98 (0.4-24.7)	**Gender (self-reported)**	
		Female	137
		Male	157
		Other	1
Race (self-reported)		**Primary Service**	
American Indian/Alaska Native	1	Hematology	15
Asian	10	Infectious Diseases	15
Black	88	Leukemia/Lymphoma	76
White	182	Neuro Oncology	78
Mixed Race or Other	14	Radiation Oncology	23
		Solid Tumor	75
		Transplant and Cellular Therapy	13
Reason for Visit Initiation		**Visit Location**	
Legal Guardian Request	9	Inpatient	7
Pharmacogenomics Program	284	Outpatient Clinic	288
Prescriber Request	2		

Clinic Visits Typically Last 25 Minutes



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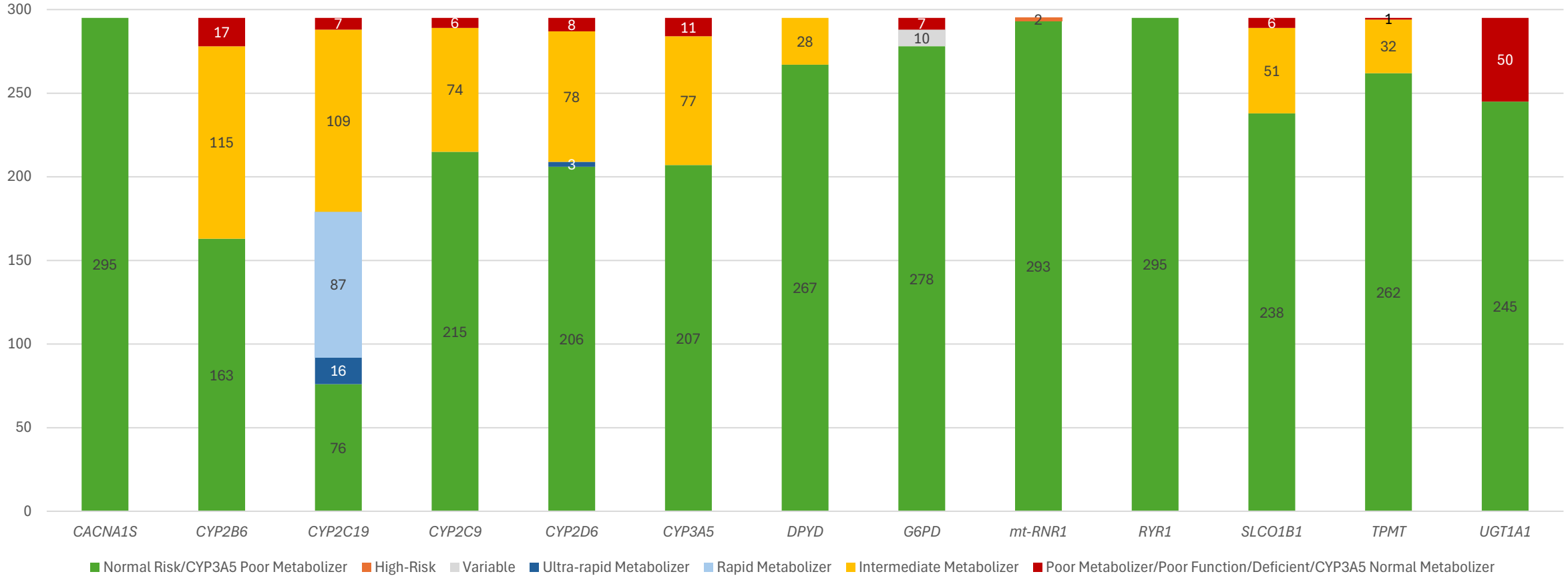
n=295 as of 02/01/2025

Patients Seen in Clinic Have a Median of 3 Actionable Pharmacogenomic Test Results



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n=295 as of 02/01/2025

Total of 15 Patients Receiving a High-risk Medication at Time of Counseling

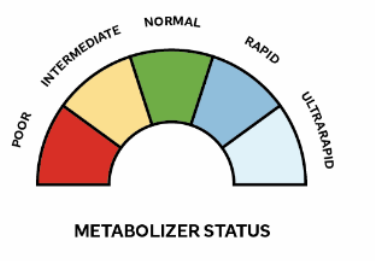
Patients Receiving Actionable Medication at Time of Counseling (recommended therapy modification)	
Mercaptopurine (30% dose reduction)	7
Voriconazole (monitor serum concentrations)	2
Amitriptyline (monitor for efficacy)	1
Irinotecan (monitor for toxicity)	1
Ondansetron (monitor for efficacy)	1
Pantoprazole (50% dose increase)	1
Omeprazole (50% dose increase)	1
Warfarin (monitor INR)	1

All medications were appropriately dose adjusted, or close monitoring based on recommendations in clinical decision support alerts

Education Summary Shared with Patients During Clinic Visit

Introduction

Pharmacogenomic test results help your medical team know the best type of medicine or the correct dose of a drug for you. We do these tests to make some medications safer and more effective for you. Pharmacogenomic test results last a lifetime because genes do not change. Your doctors and pharmacists can always use the results. This can help your medical team pick the best medicines for you in the future. Save any pharmacogenomic test results you get. Tell your other doctors and pharmacists that pharmacogenomic testing has been performed and let them know the results. Pharmacogenomic test results will also be stored in your child's medical record.



METABOLIZER STATUS

When you take a medicine, your body needs a way to handle it. One way your body does this is (metabolize) the medicine. If you break down a medicine too fast or too slow, the medicine may more side effects. In some instances, a small number of people will have unknown function, whic indeterminate.

Part I: Result Summary

Gene	Genotype	Phenotype
CACNA1S	*WT/WT*	CACNA1S Malignant Hyperthermia Variant Negative
CYP2B6	**1/*1*	CYP2B6 Normal Metabolizer
CYP2C19	**1/*17*	CYP2C19 Rapid Metabolizer
CYP2C9	**1/*1*	CYP2C9 Normal Metabolizer
CYP2D6	*(*2/*2)2N*	CYP2D6 Normal Metabolizer
CYP3A5	**1/*3*	CYP3A5 Intermediate Metabolizer
DPYD	*c.=/c.=*	DPYD Normal Metabolizer
G6PD	*B/Null*	G6PD Normal
*HLA-B *57:01*	*Negative*	HLA-B*57:01 Negative
MT-RNR1	*WT*	MT-RNR1 Normal Risk of Aminoglycoside-Induced Hearing Loss
RYR1	*WT/WT*	RYR1 Malignant Hyperthermia Variant Negative
SLCO1B1	**1/*37*	SLCO1B1 Normal Function
TPMT	**1/*1*	TPMT Normal Metabolizer
UGT1A1	**28+80/*28+80*	UGT1A1 Poor Metabolizer

Education Summary Shared with Patients During Clinic Visit

Introduction

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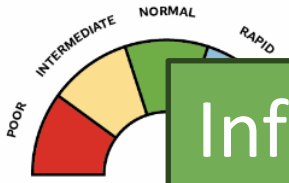

METABOLIZ

When you take a medicine, your body needs a way to handle it. One
(metabolize) the medicine. If you break down a medicine too fast or
more side effects. In some instances, a small number of people will
indeterminate.

Part I: Result

MT-RNR1	*WT*	MT-RNR1 Normal
RYR1	*WT/WT*	RYR1 Malignant H
SLCO1B1	*1/*37	SLCO1B1 Normal
TPMT	*1/*1	TPMT Normal Me
UGT1A1	*28+80/*28+80	UGT1A1 Poor Met

Inform your doctors and pharmacists of the results when asked about allergies

Part II: Result Details

Gene	Genotype	Phenotype
CACNA1S	*WT/WT*	CACNA1S Malignant Hyperthermia Variant Negative

CACNA1S is a gene that can increase the side effects of certain medicines. Differences in your DNA determine whether the changes in the *CACNA1S* gene will increase a person's risk of side effects after receiving anesthesia. People who are in the "CACNA1S Malignant Hyperthermia
ment of medicines (such as
genotype test result.
notype test result. For more

Phenotype
CYP2B6 Normal Metabolizer

medicines. Differences in your DNA determine how well the CYP2B6 enzyme will break down certain medicines. People who are CYP2B6 normal metabolizers have normal amounts of CYP2B6 enzyme. They don't normally need dosage adjustments of medicines (such as methadone or efavirenz) based on *CYP2B6* genotype test result. For more information, review the CYP2B6 and Medicines education page.

Gene	Genotype	Phenotype
CYP2C19	*1/*17	CYP2C19 Rapid Metabolizer

CYP2C19 is an enzyme that is responsible for breaking down or activating certain medicines. Differences in your DNA determine how well the CYP2C19 enzyme will break down or activate certain medicines. People who are CYP2C19 rapid metabolizers have slightly increased amounts of CYP2C19 enzyme. They may need to have the dose of some medicines increased to achieve the desired effect of the medicine (such as omeprazole and lansoprazole). There are other medicines affected by CYP2C19. For more information, review the CYP2C19 and Medicines education page.

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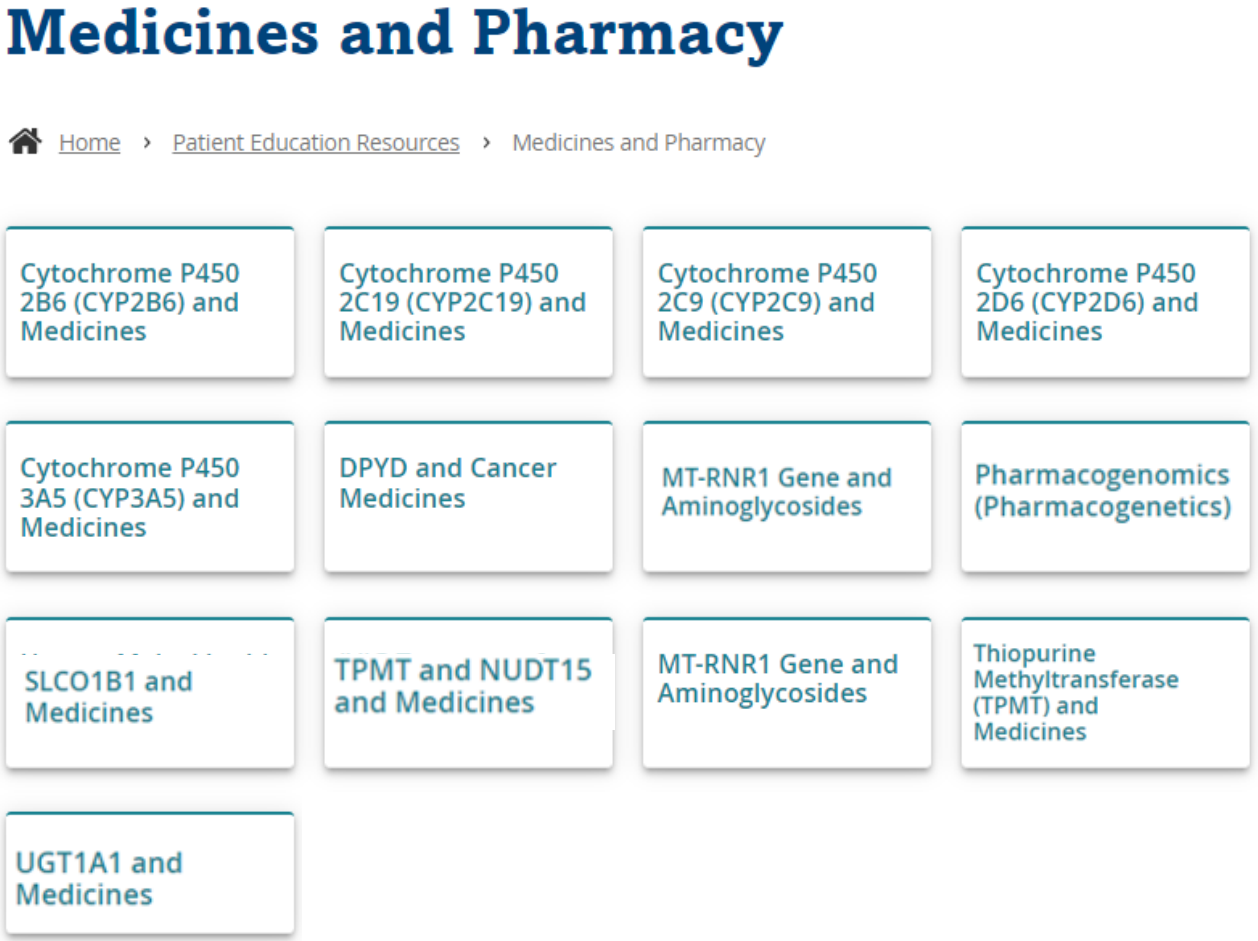
Gene-Specific Patient Educational Material

Also available in Spanish

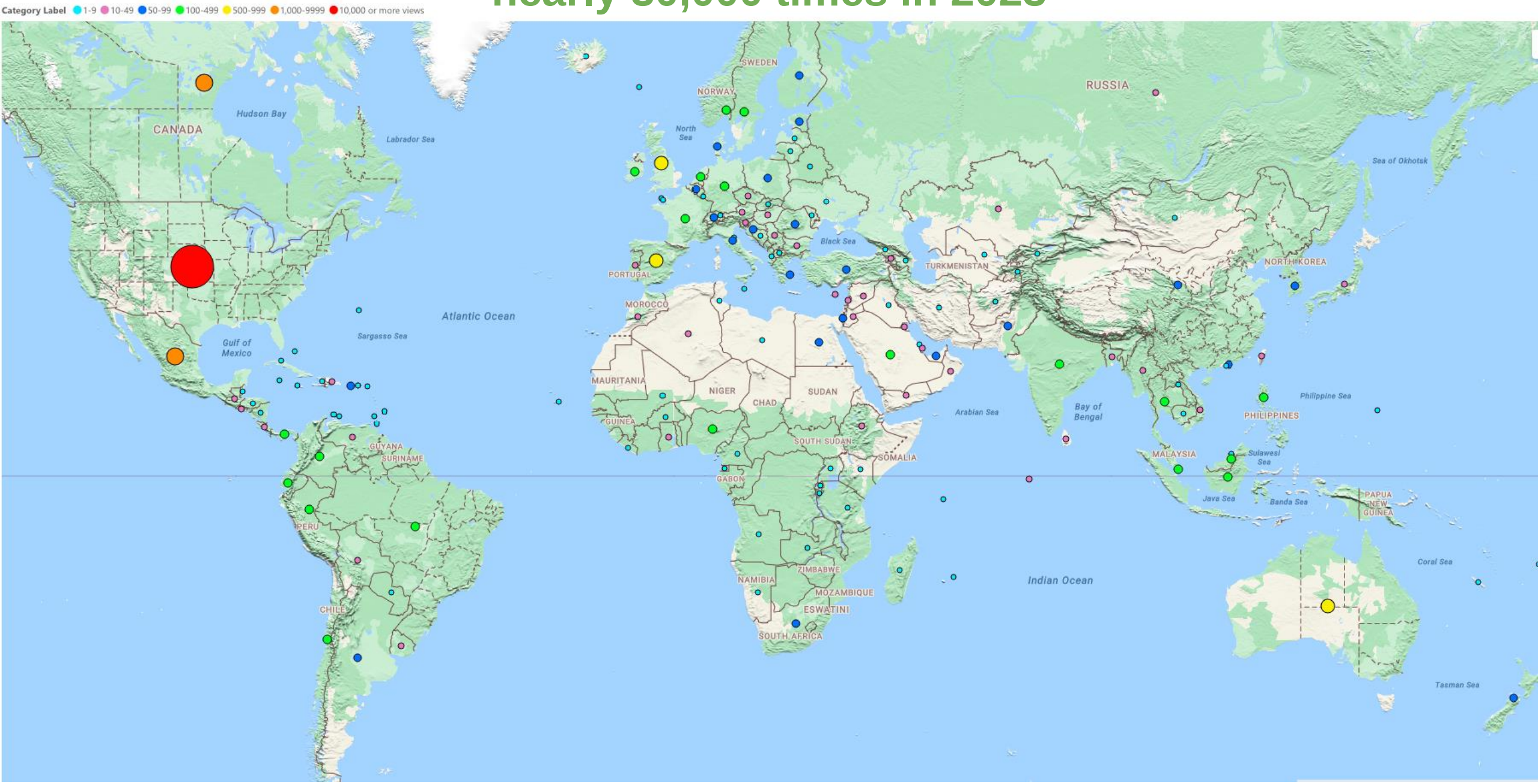
CHILDREN'S ONCOLOGY GROUP

www.together.stjude.org

Pharmacogenomics Educational Material on St. Jude/Together Website



St. Jude pharmacogenomic online educational resources were accessed nearly 30,000 times in 2023



Patients are Approached Several Times for Pharmacogenomic Discussions

How Can Patients Review Pharmacogenomic Test Results?

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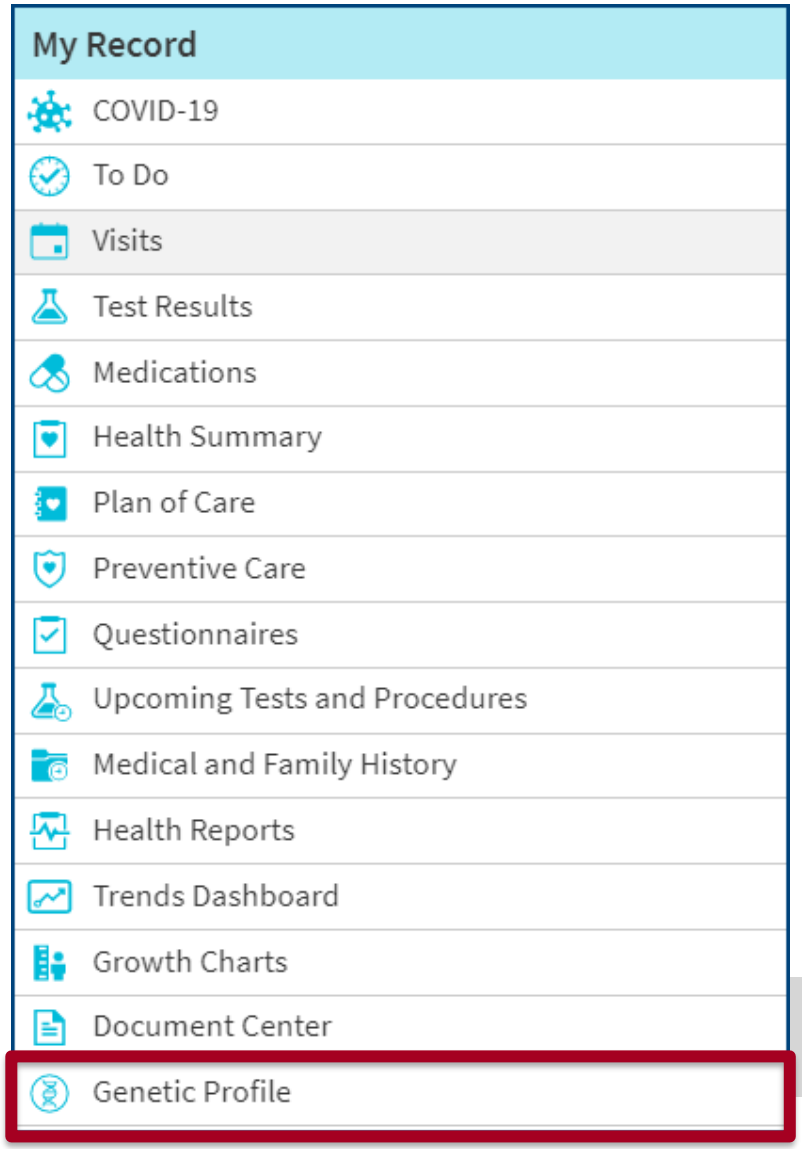
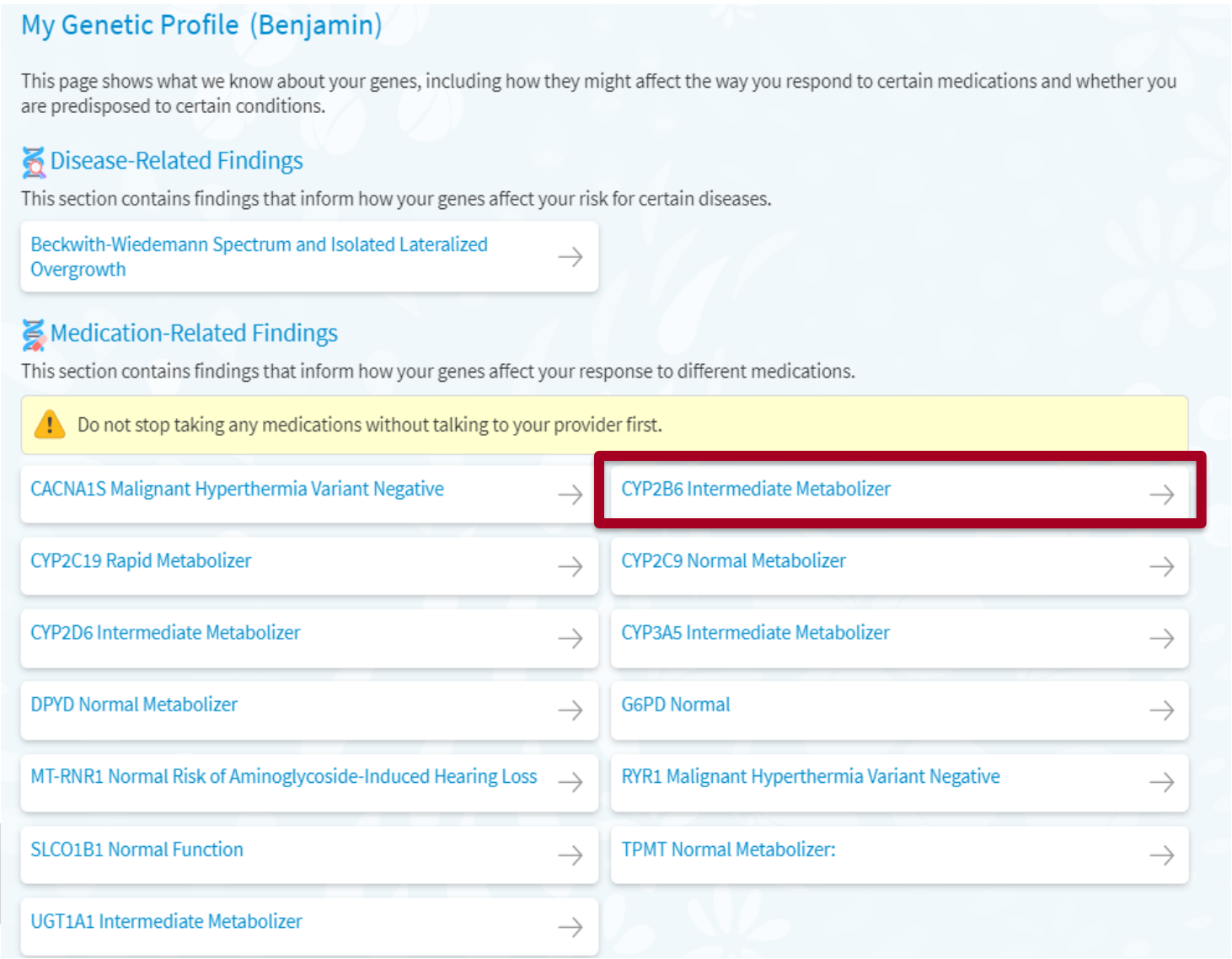
Patients Access to Pharmacogenomic Test Results in MyChart Through Genetic Profile



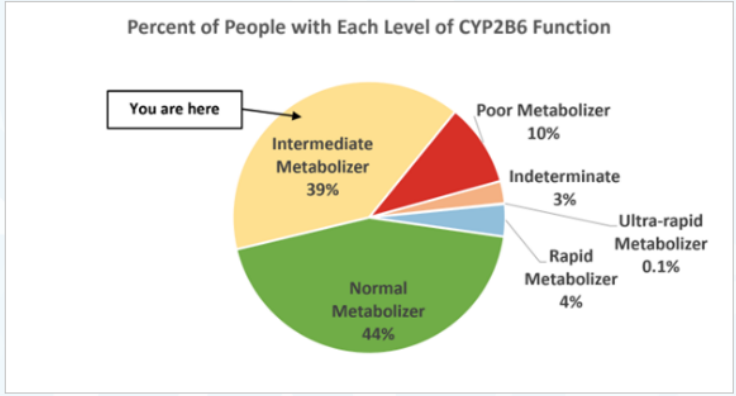


More Detailed Information About Each Phenotype

CYP2B6 Intermediate Metabolizer (Benjamin)

This test was performed during your treatment at St. Jude Children's Research Hospital to look for variations (changes) in certain genes. A gene refers to a part of the DNA. Variations in genes may affect how well you respond to certain medicines. Because your genes stay the same even as you age, it is important for you to share this result with your other doctors and pharmacists outside St. Jude. Those providers may not have easy access to all the information in your St. Jude medical record. This result may affect how doctors prescribe medicines throughout your life.

You are predicted to be a CYP2B6 intermediate metabolizer. People in this group have lower CYP2B6 enzyme function. You will likely need a different dose of some medicines or possibly a different medication. This result impacts the medication efavirenz. Please check with your doctor or pharmacist if you are unsure about whether you are taking this medication. Even though you may not be receiving a medicine related to CYP2B6 right now, you may receive them in the future. You have the same gene status as about 39% of people, as shown in the chart below. The exact percentage of each group varies by ethnic group, see www.stjude.org/CYP2B6.



You might have had genetic testing performed for other reasons. The Cancer Predisposition Clinic might have tested you to see if you are at risk for a disease that can be passed down in families (hereditary). Please talk to your doctor or genetic counselor for the results of those other tests.

For details on how to understand your *CYP2B6* gene test result and your other gene test results that affect medications, visit www.stjude.org/pg4kds. For more information, you may also visit http://cpicpgx.org/gene/cyp2b6/

If you have questions about your gene test result, email pharmacogenomics@stjude.org *or* call St. Jude research nurses at 901-595-2482. If you are calling from outside the Memphis area, dial toll-free 1-866-2ST-JUDE (1-866-278-5833), and ask for extension 2482.

⚠ Do not stop taking any medications without talking to your provider first.

Related Test Results

CYP2B6 PG4KDS GENOTYPE on Oct 22, 2024

ARS Question

When counseling patients about their pharmacogenomic test results, it is important to discuss which of the following?

A. The lifelong implications of the result

B. Importance of sharing results with new clinicians

C. Important of sharing result with pharmacists

D. All of the above

Clinical Implementation

Feasible in pediatric oncology setting

Patient Education

Is crucial

Need to emphasizes importance of sharing results

Mary Relling

Kristine Crews

James Hoffman

Allison Bragg

Kate Collum, Don Baker & **Clinical Informatics**

Kelly Caudle

Andrew Pappas, Ben McKinley, Nancy Kornegay, Ben McKinley, Austin Springer, Mark Wilkinson

Wenjian Yang, Colton Smith

Alejandro Molinelli & **PK Clinical Laboratory**

- Jun Yang
- Cheng Cheng
- Michael Rossi
- Clifford Takemoto
- **Genetic Counselors:** Rose McGee, Sara Lewis, Alise Blake, Lily Grieve, Passant Shaker, Arti Pandey
- **Pharmacists**
- **Clinical Staff**
- **Current and former clinical pharmacogenomics residents:** Kevin Hicks, Gillian Bell, Mark Dunnenberger, Rose Gammal Donnelly, Amy Pasternak, Jennifer Hockings, Cameron Thomas, Keito Hoshitsuki, Sarah Morris, Katherine Robinson, Jenny Nguyen, Rachael Stone, Kayla Thibodaux, Meghan McNulty
- **St. Jude patients and families**

Question & Answer Session

Cyrine-Eliana Haidar, Pharm.D., BCPS, BCOP, FASHP

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Please text your attendance (within 24 hours) then complete the post-test and evaluation (within 4 weeks) at https://stjude.cloud-cme.com/COG **or contact cpe@stjude.org with questions)**

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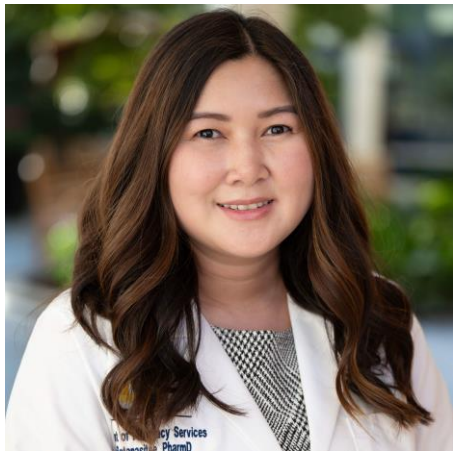
Fear of Fever: Bacterial Infection Rates and Antibiotic Use During Dinutuximab for High-Risk Neuroblastoma



Kelly Ratanasitee, PharmD
PGY-2 Pediatric Pharmacy Resident

Madeleine King, PharmD, BCOP
Project Mentor

University of Michigan, Ann Arbor, MI

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Conflicts of Interest/Disclosures

NAME	COMPANY	RELATIONSHIP
Kelly Ratanasitee, PharmD	Nothing to disclose	
Madeleine King, PharmD, BCOP	Nothing to disclose	

All relevant financial relationships listed for the individual have been mitigated by the ACPE accredited provider (St. Jude Continuing Pharmacy Education Program).

Learning Objective

- Evaluate the incidence of bacterial infections in febrile pediatric patients with high-risk neuroblastoma receiving dinutuximab to assess the need to continue to administer broad-spectrum antibiotics

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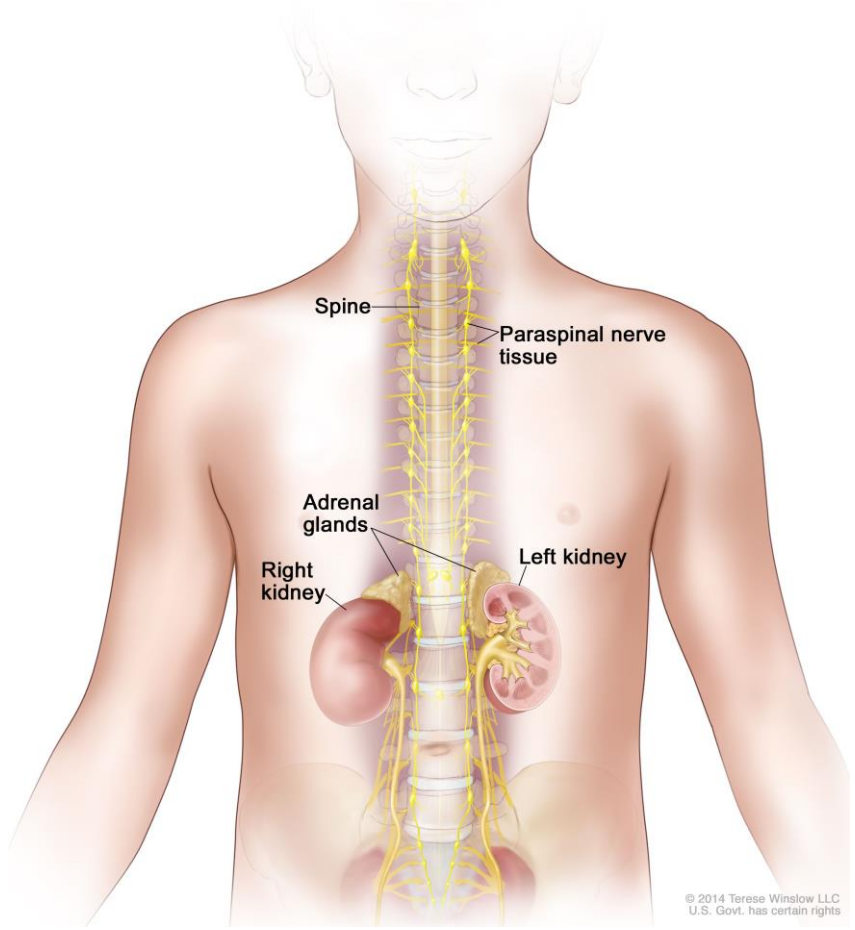
Off-label Use Disclosure: This session does not include a discussion of off-label treatment and investigational agents not approved by the FDA for use in the US.

Neuroblastoma Overview

- Most common extracranial solid tumor occurring in pediatric patients
- Arises in adrenal medulla and paraspinal region where sympathetic nervous system tissue is present
- Management based on risk stratification



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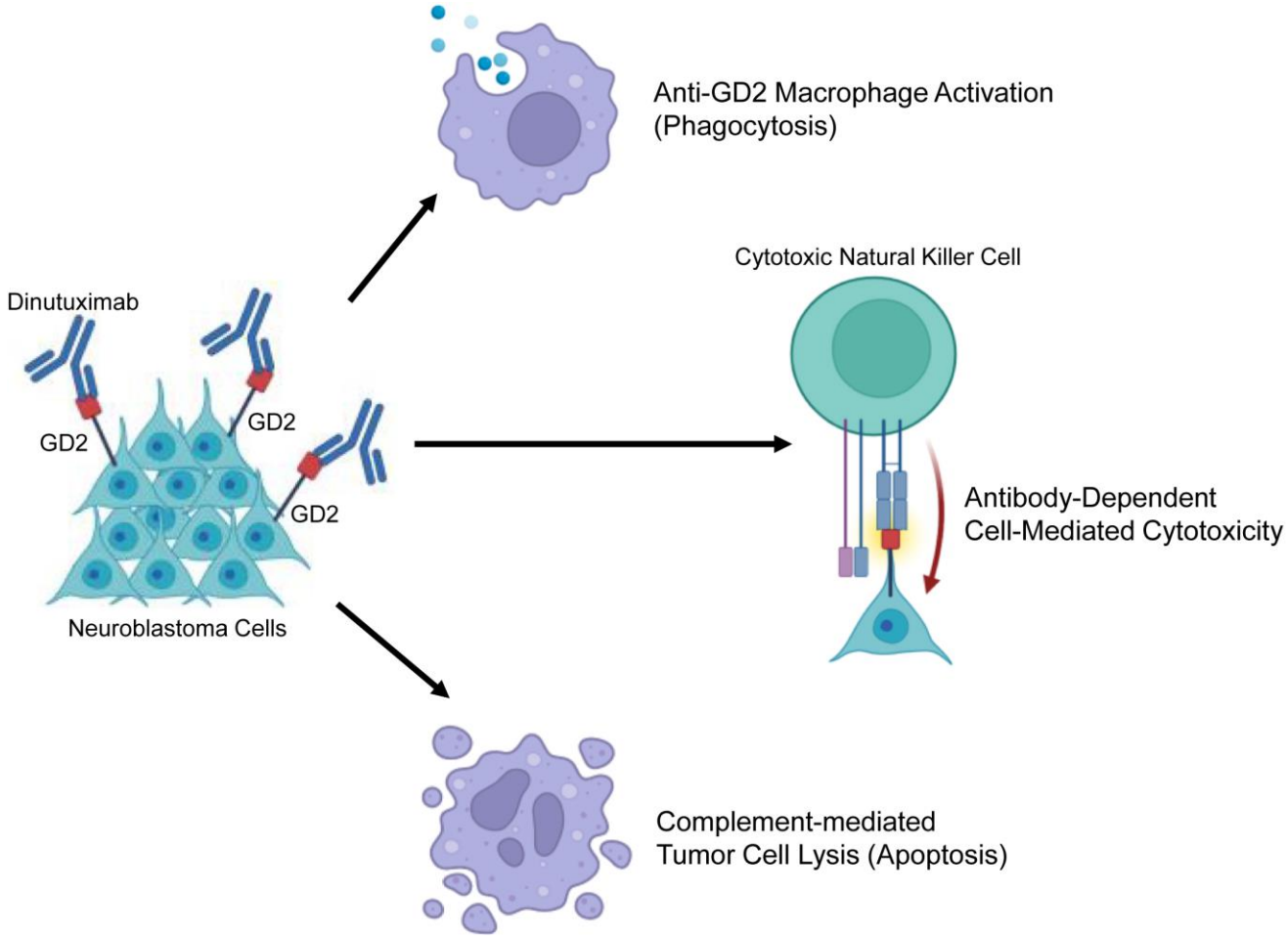
Matthay KK. *Nat Rev Dis Primers*. 2016;2(16078):1-21.
National Cancer Institute. Neuroblastoma Treatment (PDQ®) - Health Professional Version.

Dinutuximab

- Used in post-consolidative therapy or relapse of neuroblastoma
- Monoclonal antibody targeting glycolipid disialoganglioside (GD2) on neuroblastoma cells
- Common adverse effects include infusion reaction, neurotoxicity, pain, capillary leak syndrome, and fever



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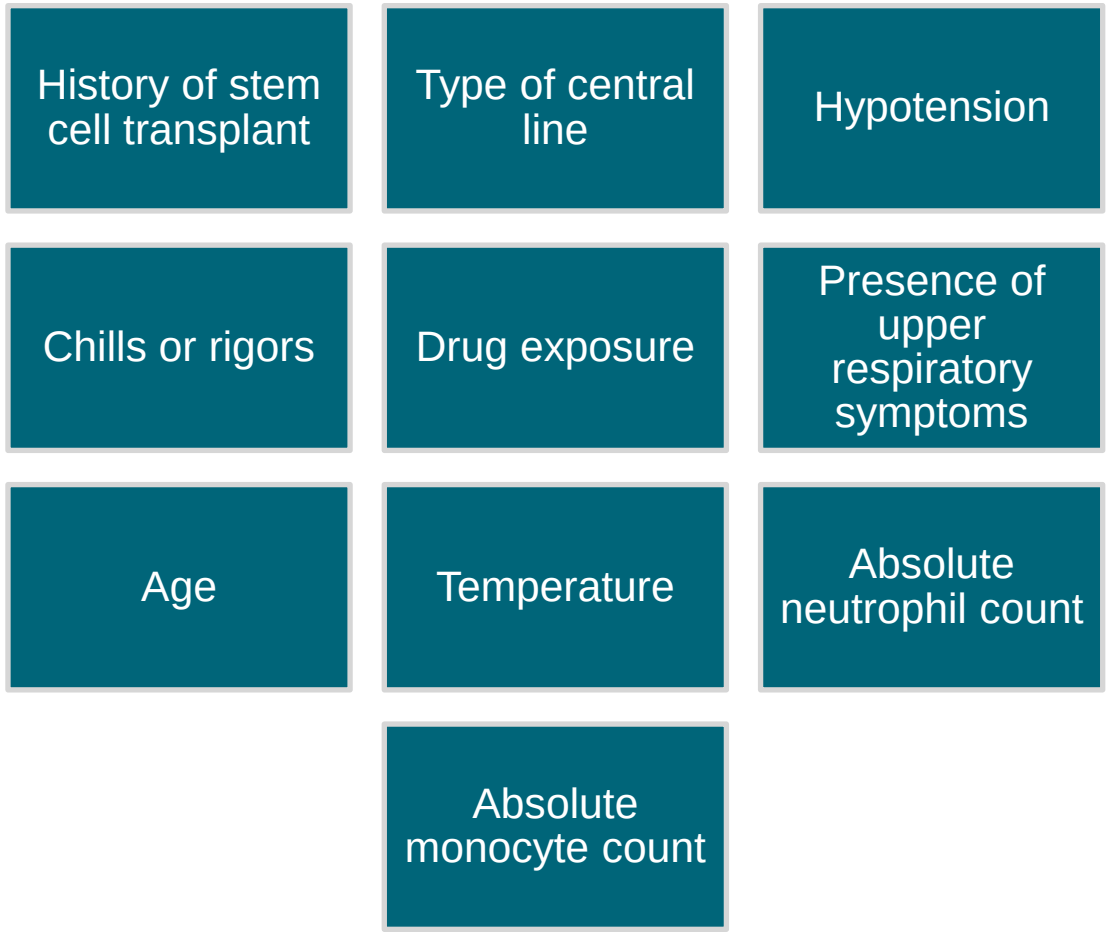
Barone G. *Paediatr Drugs*. 2021;23(6):537-548.
Lee WG. *Surg Oncol Clin N Am*. 2024;33(2):409-446.
Unituxin (dinutuximab injection) [package insert]. Silver Spring, MD: United Therapeutics Corp.; 2015.

Current Institutional Practice

Predictors for Blood Stream Infections in Pediatric Oncology Patients

- Esbenshade/Vanderbilt (EsVan) model
  - Included febrile pediatric oncology patients without severe neutropenia
- Antibiotics warranted if predicted risk of bloodstream infection >40%



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Esbenshade AJ. *Cancer*. 2017;123(19):3781-3790.

Active Learning Question

JF spikes a 39°C fever 24 hours after starting dinutuximab infusion. She is not neutropenic and appears clinically stable. What would your next course of action be?

A. Recommend starting cefepime

B. Recommend starting ceftriaxone

C. Nothing, just watch and wait

D. Admit to pediatric intensive care unit (PICU)

Study Aims

Determine the incidence of bacterial infections for high-risk neuroblastoma patients who develop fever during administration of dinutuximab

Identify risk factors for documented bacterial infection to further refine the need for repeated use of broad-spectrum antibiotics during hospital admissions for dinutuximab

Methods

Study design	• Single-center, retrospective study from September 1, 2019 to August 30, 2024
Inclusion criteria	• Patients with high-risk neuroblastoma who developed a fever within 48 hours of dinutuximab administration
Exclusion criteria	• Fever within 48 hours prior to dinutuximab administration • Receiving treatment for a documented infection within 48 hours prior to dinutuximab administration • Receiving concurrent aldesleukin therapy

Methods

Statistical analysis

- Baseline demographics and data analyzed using descriptive statistics
- Parametric data analyzed using T-test
- Non-parametric data analyzed using Chi-square or Fishers Exact test
- Univariate and multivariate logistic regressions to identify independent risk factors for bacteremia

Study Outcomes

Primary outcome

- Incidence of bacteremia

Secondary outcomes

- Duration of antibiotic course
- Fever duration
- Length of hospital stay
- PICU admission
- Death during admission
- Risk factors for developing bacteremia

Results

37 patients identified with 364 encounters of dinutuximab

37 patients with 177 encounters of dinutuximab analyzed

187 encounters excluded

No fever during dinutuximab administration	179 (96%)
Treatment for documented infection within 48 hours of dinutuximab	8 (4%)

*All data presented as n (%)

Results – Baseline Characteristics

Baseline Characteristics (n=37)	
Sex (male)	21 (56.8%)
Ethnicity	
Hispanic or Latino	5 (13.5%)
Not Hispanic or Latino	32 (86.5%)
Race	
Caucasian	33 (89.2%)
Black or African-American	3 (8.1%)
Unknown or not reported	1 (2.7%)
History of autologous stem cell transplant	28 (75.7%)

*All data presented as n (%)

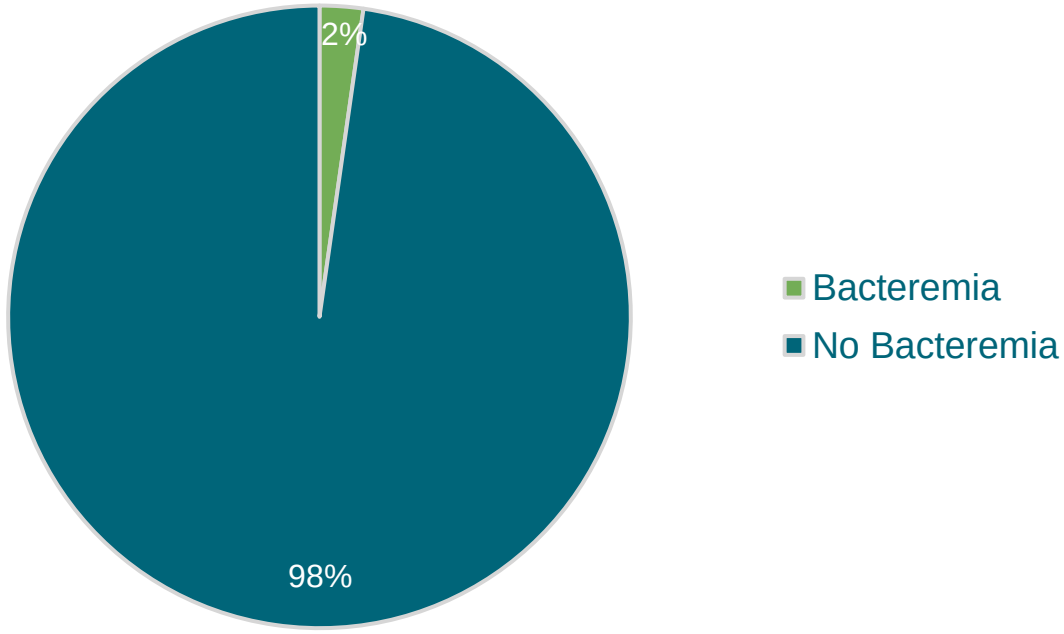
Results – Baseline Characteristics

Baseline Characteristics (n=177)	
Age (years)	4.06 (2.84, 6.78)
Dinutuximab indication	
Post-consolidation therapy	77 (43.5%)
Relapsed/refractory therapy	100 (56.5%)
Central line type	
Port	119 (67.2%)
PICC	6 (3.4%)
Port and PICC	20 (11.3%)
Tunneled CVC	32 (18.1%)

*All data presented as n (%) or or median (IQR: 25th percentile, 75th percentile)

Results – Primary Outcome

Incidence of Bacteremia	n (%)
True positive blood culture[1]	4 (2%)
No growth on blood culture	173 (98%)



[1]8 positive blood cultures, 4 considered contaminants

Results – Primary Outcome

	Microorganism growth	Susceptibility to ceftriaxone	Antibiotic therapy
1	*Bacillus cereus*	No susceptibilities reported	Ceftriaxone
2	*Streptococcus salivarius* *Staphylococcus homini* *Streptococcus mitis* *Coagulase negative staphylococcus*	Susceptible No susceptibilities reported Susceptible No susceptibilities reported	Ceftriaxone transitioned to vancomycin; discharged on levofloxacin
3	*Pseudomonas putida* *Janibacter hoylei*	No susceptibilities reported No susceptibilities reported	Ceftriaxone transitioned to cefepime
4	*Gordonia species* *Rhizobium radiobacter* *Acinetobacter species*	No susceptibilities reported No susceptibilities reported No susceptibilities reported	Ceftriaxone initially, vancomycin added; discharged on sulfamethoxazole-trimethoprim and ciprofloxacin

Results – Secondary Outcomes

Secondary Outcomes (n=177)	
Duration of antibiotic course, days	2.01 (1.45, 3.14)
Fever duration, days	1.82 (0.82, 3.05)
Length of hospital stay, days	5.00 (5.00, 6.00)
PICU admission	3 (1.7%)
Death during admission	0 (0%)

*All data presented as n (%) or median (IQR: 25th percentile, 75th percentile)

EsVan Model Analysis

	Central line type	Hypotensive	Shaking, chills, or rigors	History of stem cell transplant	Upper respiratory symptoms	Age (years)	Height of temperature (Celsius)	ANC	Calculated infection risk (%)
1	Port	No	No	No	No	6	39.3	>500	0.2
2	PICC	No	No	Yes	No	2	38.4	>500	1.1
3	Port	No	No	Yes	Yes	3	38.9	>500	0.2
4	PICC	No	No	Yes	No	4	40.1	>500	3.4

Study Limitations

- Retrospective, single-center study design
- Chart review was limited to detect non-culture positive infections
- Insufficient number of patients with primary outcome to run multivariable analysis for statistical significance

Conclusions

Majority of patients that fever during dinutuximab administration do not develop bacterial infections

Bacteremia incidences in this study were all central-line associated bloodstream infections

Patients that developed bacteremia did not grow organisms that ceftriaxone would have reliably treated

Future Directions

Present findings to pediatric infectious diseases and oncology groups

Adjust current institutional practice

- Draw cultures at first fever but hold off on starting antibiotics if clinically stable and not neutropenic

Learning Assessment

Which of the following statements regarding dinutuximab is true?

A. Cefepime should be used in all patients who receive dinutuximab due to the high risk of bacteremia
B. Fever is not a common adverse event observed with dinutuximab
C. The majority of patients who fever, even with risk factors for infection, do not develop bacteremia with dinutuximab
D. Dinutuximab is not used in post-consolidation or relapsed/refractory neuroblastoma

Acknowledgements

- Madeleine King, PharmD, BCOP
- Julia Brown, PharmD
- Martina Fraga, PharmD, BCOP

Question & Answer Session

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Short Course Cefixime to Prevent Irinotecan-Associated Diarrhea in Children with Solid Tumors

Megan Wright, PharmD, BCPS

Clinical Pharmacy Specialist

St. Jude Children's Research Hospital in Memphis, TN

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Conflicts of Interest/Disclosures

- There are no relevant financial interests in the last 24 months to disclose for any person with control over the content of this presentation

All relevant financial relationships listed for the individual have been mitigated by the ACPE accredited provider (St. Jude Continuing Pharmacy Education Program).

Learning Objectives

- Review literature surrounding the use of cefixime for irinotecan-associated diarrhea
- Discuss considerations for shortening prophylaxis duration
- Describe practice changes and results of implementation

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Off-label Use Disclosure: This session does include a discussion of off-label treatment not approved by the FDA for use in the US.

Irinotecan

Pharmacological Class

- Topoisomerase I inhibitor

Dosing

- Pediatric Sarcomas: 50 mg/m^2 IV daily *or* 90 mg/m^2 PO daily for 5 days, every 21 days

Adverse Effects

- Cholinergic syndrome, nausea, vomiting, myelosuppression
- **Diarrhea** (severe 10 to 18%)

IV: Intravenous PO: By Mouth

Irinotecan. Lexi-Drugs. Hudson, OH: Le

Mechanism of Diarrhea

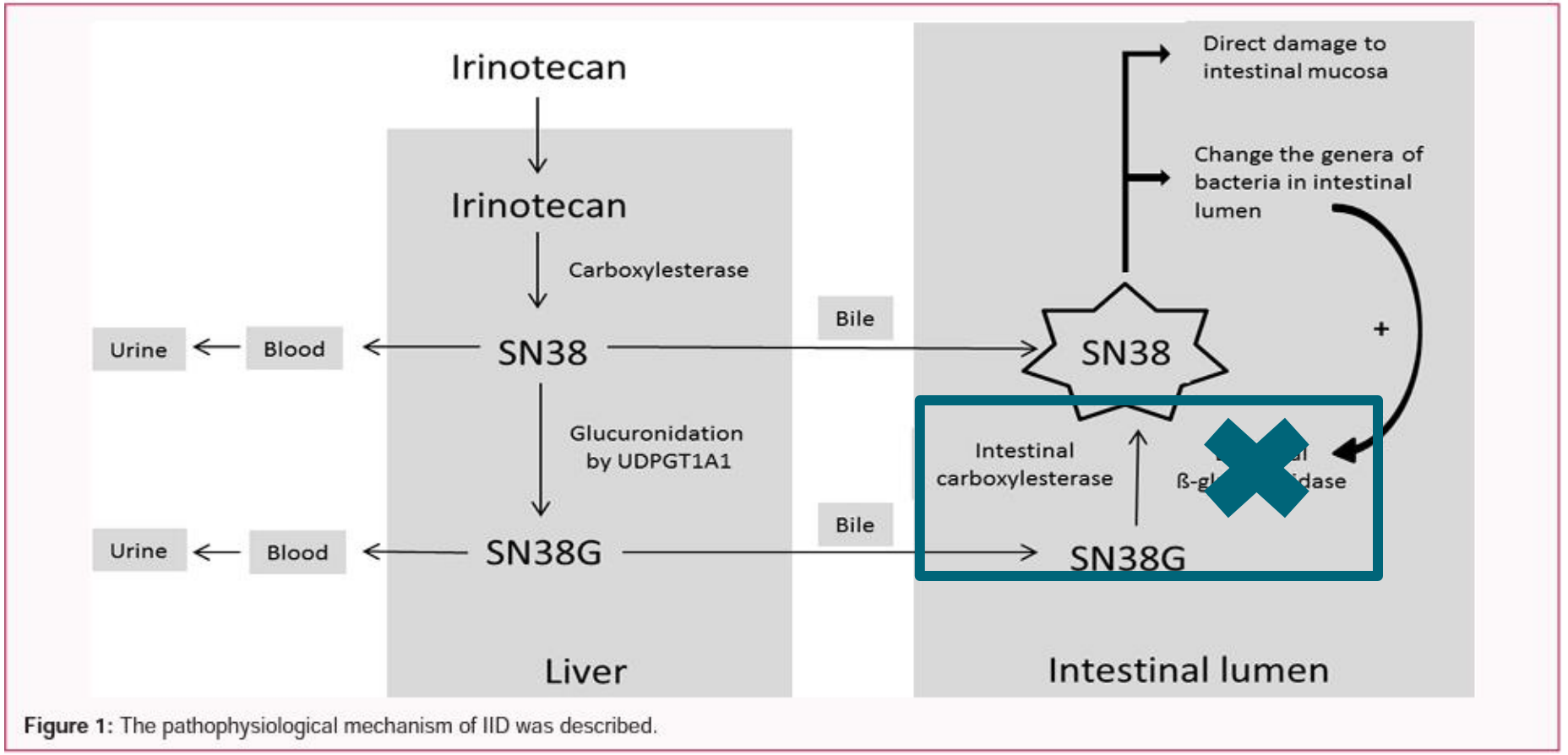

Figure 1: The pathophysiological mechanism of IID was described.

Xu J, et al. *Clin Oncol*. 2022; 7: 1953.

Cefixime Allows for Dose Escalation of Irinotecan

Furman, et al.	
Objectives	• Determine the MTD, dose-limiting toxicity and pharmacokinetics of oral irinotecan • Evaluate whether coadministration of cefixime 8 mg/kg/day, 5 days prior and continued during irinotecan therapy, reduced irinotecan-associated diarrhea
Inclusion Criteria	• <21 years of age • Diagnosis of recurrent solid tumor, for which conventional treatment had failed

Results	Enrolled 39 patients
	• 19 patients were treated with cefixime
	  • MTD of irinotecan was 1.5x higher at 60 mg/m^2 daily for 5 days for 2 consecutive weeks (repeated every 21 days)
	  • No patients complained or inability to tolerate cefixime

Conclusion	Cefixime administration with irinotecan was well tolerated and allowed for greater dose escalation

Moving Forward: What is the optimal duration of cefixime?

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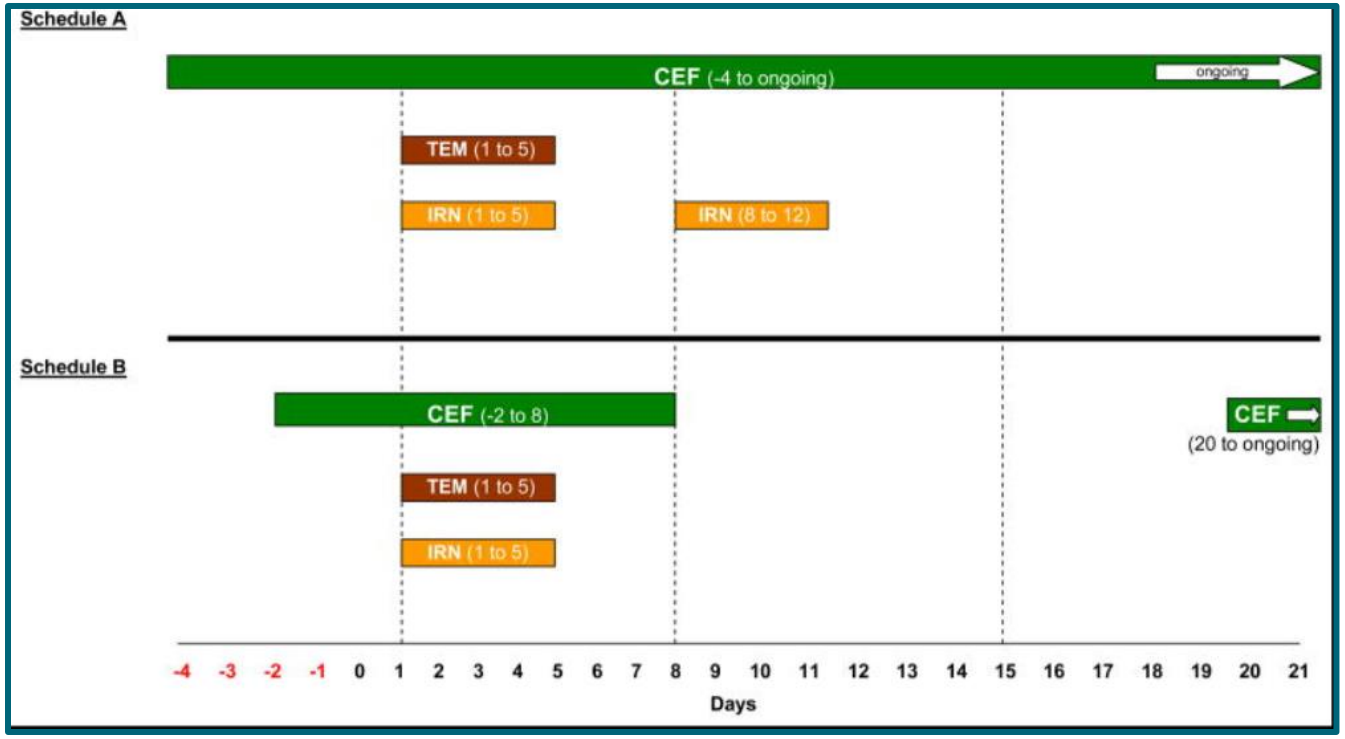
MTD: maximal tolerated dose

Furman WL, Crews KR, Billups C, et al. *J Clin Oncol*. 2006;24(4):563-570.

Shortened 5-day course of Irinotecan with 10-day course of Cefixime resulted in greater dose intensity of Irinotecan



Results	• Enrolled 42 patients, with 36 available for toxicity analysis
	• Non-Hematologic DLT:
	  • Overall Grade 3 diarrhea: 11%
	  • Schedule A vs. Schedule B Grade 3 Diarrhea: 3 vs. 1

Conclusion	The 5-day schedule of VOIT was well tolerated and allowed for greater dose intensity of irinotecan and temozolomide

COG Standard of Care: Initiation 2 days prior to irinotecan, during irinotecan administration and continued 3 days after

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CEF: Cefixime TEM: Temozolomide IRN: Irinotecan
DLT: Dose Limiting Toxicity COG: Children's Oncology Group

Wagner LM, Perentesis JP, Reid JM, et al. *Pediatr Blood Cancer*. 2010;54(4):538-545.

Internal Review

- In 2019, evaluated 29 patients for 66 courses of irinotecan and 61 courses of cefixime
  - 3.2% compliance to COG recommendations
  - 49% of patients received cefixime for ≥ 14 days
  - No significant/severe GI sequelae discovered in those with short courses

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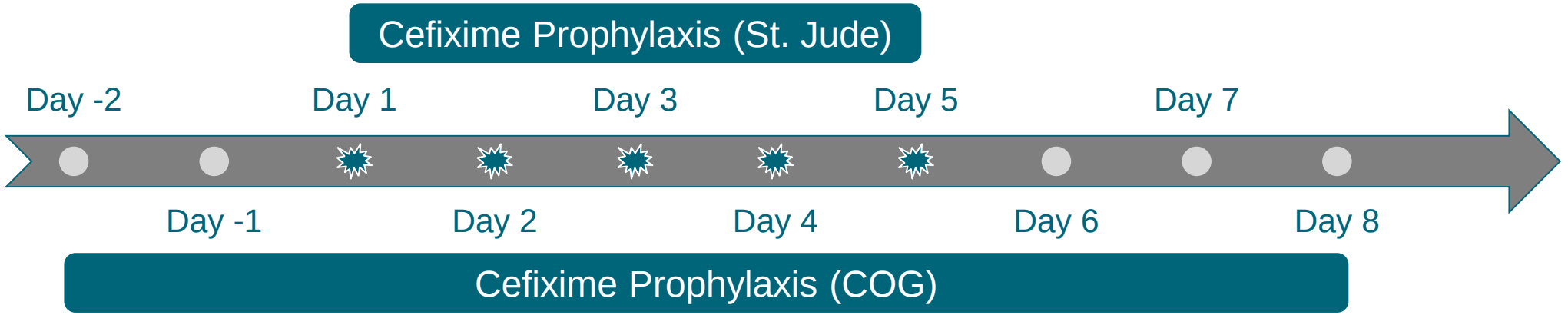
MUE: Medication Use Evaluation
EHR: Electronic Health Record

Current Practice

- Implemented on January 20, 2022
  - **First Line:**
    - Administration on the same days of irinotecan
    - Limited to total duration of 5 days
  - **Development of Severe Diarrhea:**
    - Can extend out to 10 days



Audience Participation

- What is your institution's current prophylaxis practice?
  a. Ten Days: 2 days before, 5 days during, 3 days after
  b. Eight Days: 5 days during, 3 days after
  c. Seven Days: 2 days before, 5 days during
  d. Five Days: 5 days during only
  e. No prophylaxis
  f. Other, *please explain in chat*

Audience Participation

- Please identify any compliance issues within your institution.
  a. Family inappropriately administering
  b. Delays in therapy due to counts
  c. Incorrect prescriptions from providers
  d. Poor tolerance of cefixime
  e. Other, *please explain in chat*

Study Overview

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Objectives

Primary Objective

- Compare the incidence of severe diarrhea with a course of irinotecan before and after the implementation of short-course cefixime prophylaxis

Secondary Objectives

- Evaluate provider adherence with a recently implemented standard for cefixime utilization for the prevention of irinotecan-associated diarrhea
- Compare the median number of days of cefixime prescribed per course of irinotecan during the pre- and post-implementation period
- Compare the incidence of *Clostridioides difficile* colitis or ceftriaxone-resistant infections within 21 days of receipt of irinotecan during the pre- and post-implementation period

Inclusion Criteria

- Received a 5-day course of irinotecan from a provider at St. Jude Children's Research Hospital

Pre-Intervention	• January 1, 2019, to December 31, 2019
Post-Intervention	• January 22, 2020, to May 31, 2021

Statistical Analysis

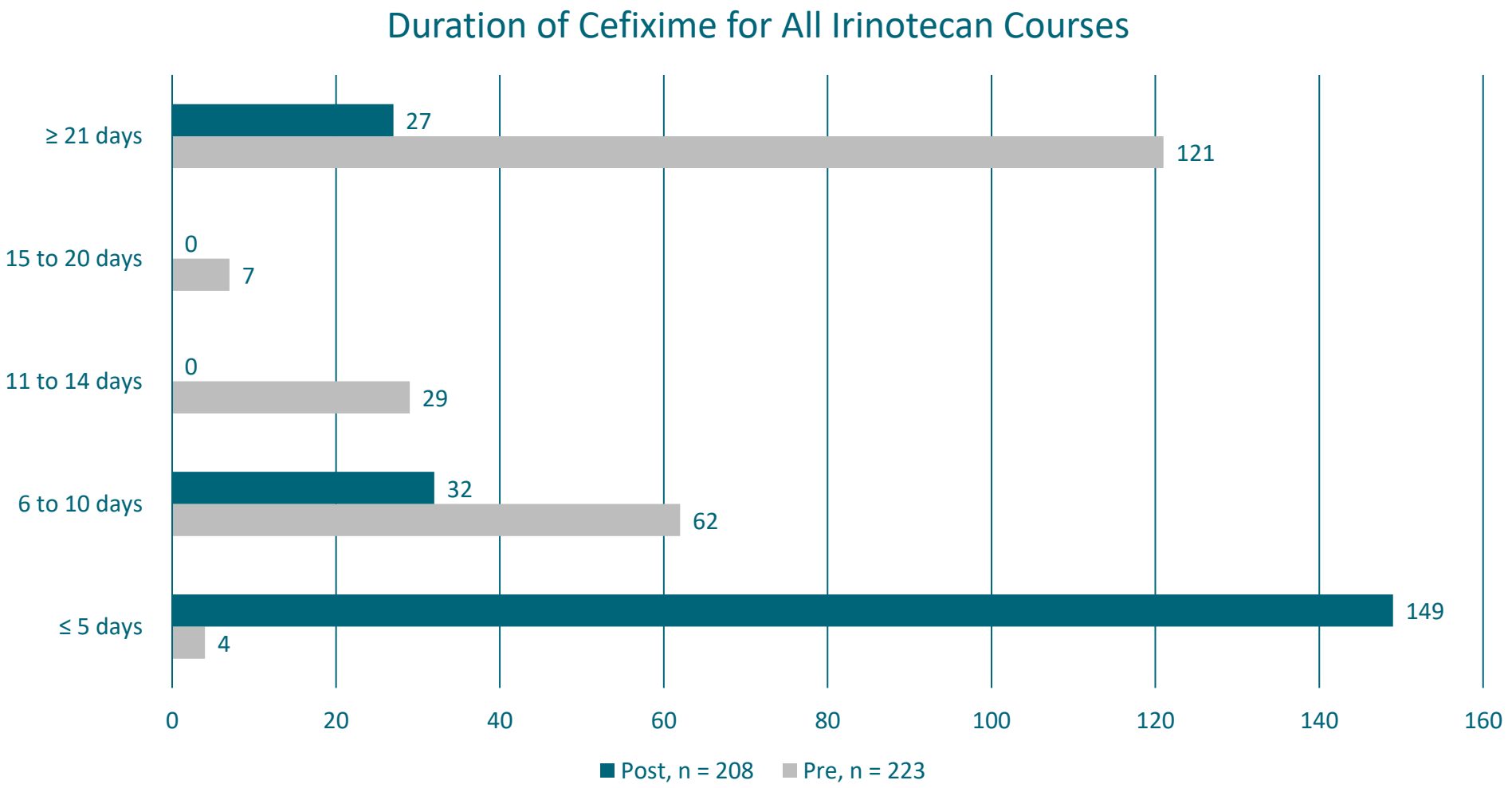
Conducted using SAS 9.4

- Analyzed all courses of irinotecan
- Numeric values were reported using median and range
- Non-parametric Wilcoxon rank-sum test was preformed between two groups
- Chi-square test and Fisher's exact test were used for categorical variables

Baseline Characteristics

Table 1. Patient Characteristics	Pre-Implementation n = 35	Post-Implementation n = 50
Median Age at Start of Irinotecan, years [IQR]	11.8 [8, 14.2]	13.3 [6.2, 17.0]
Gender, Male (%)	54%	52%
Diagnosis		
Rhabdomyosarcoma	46%	40%
Neuroblastoma	20%	30%
Other	34%	30%
UGT1A1 Phenotype		
Normal	31%	42%
Intermediate	54%	26%
Poor	9%	8%
Other	6%	14%
Irinotecan Administration Route, # of Courses (%)	**n = 208**	**n = 223**
Intravenous	164 (74%)	148 (71%)
Oral	44 (20%)	58 (28%)
Combination	15 (7%)	3 (1%)

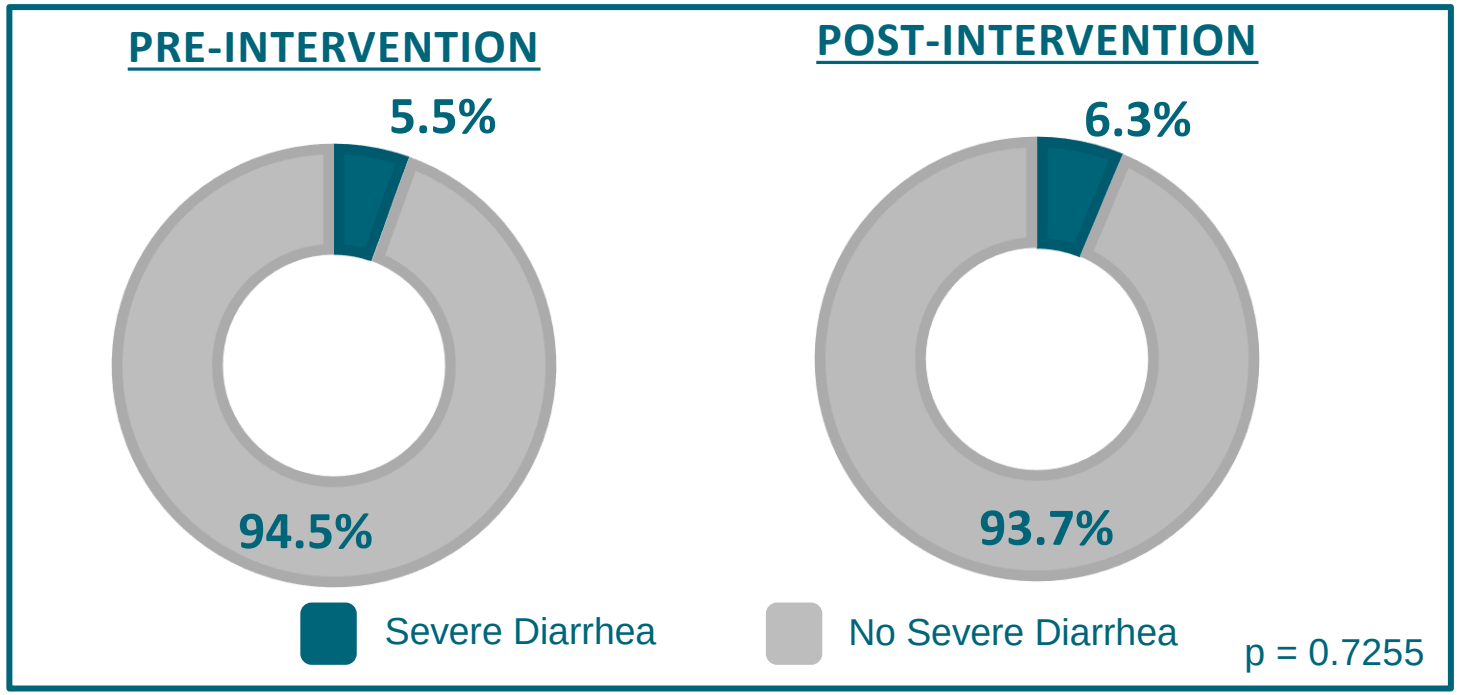
Baseline Characteristics



Severe Diarrhea Not Appreciably Different

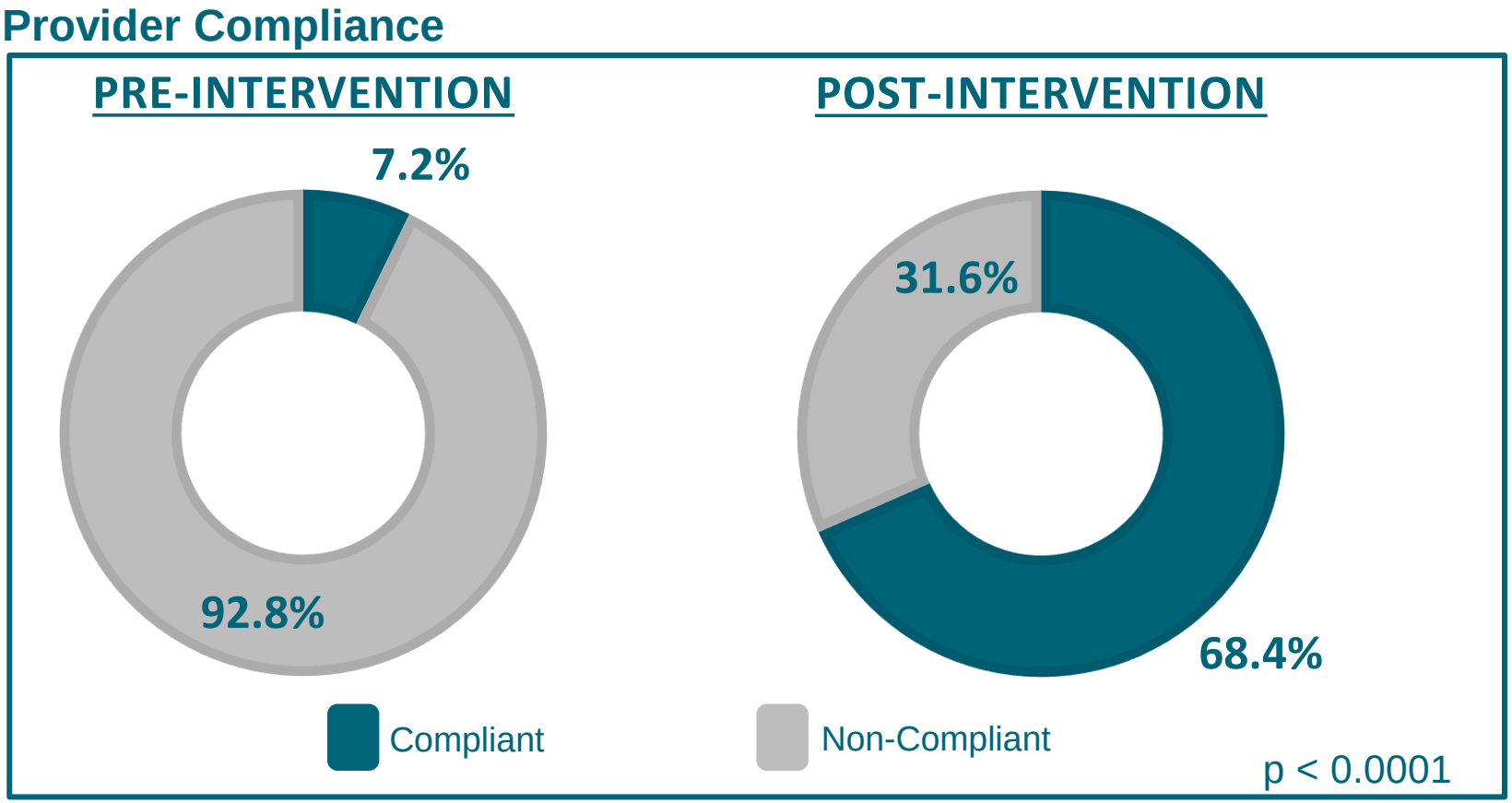
Severe Diarrhea: need for hospitalization, intravenous (IV) fluid support or total parenteral nutrition support

Incidence of Severe Diarrhea



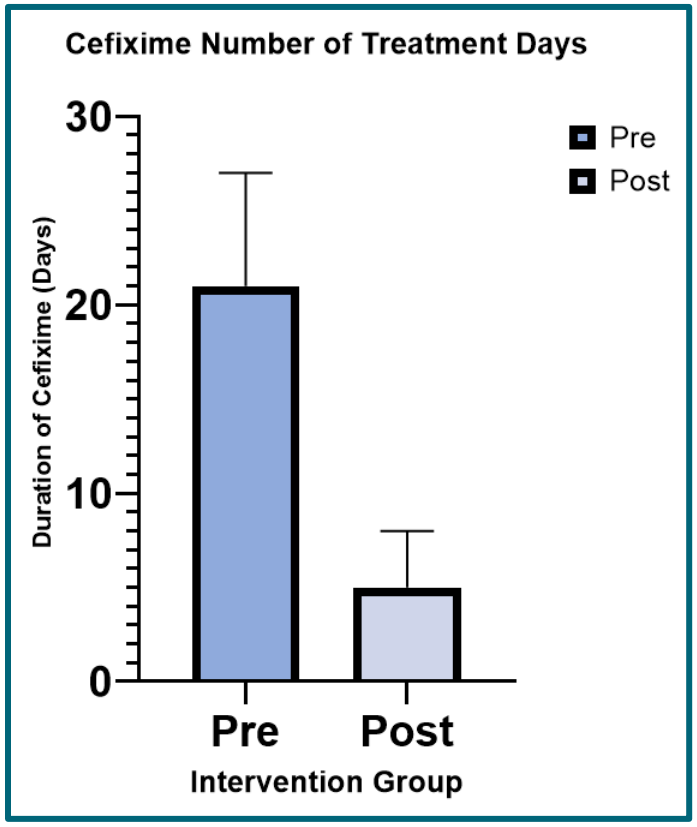
CTCAE: Common Terminology Criteria for Adverse Events

Provider Prescribing Compliance Increased



Antimicrobial Stewardship Outcomes

Duration of Cefixime



Secondary Outcomes	Pre-Implementation n = 35	Post-Implementation n = 50	p-value
Median Days of Therapy [IQR]	21 [5, 27]	5 [4,8]	p < 0.0001
C. difficile Infections, no. (%)	1 (3%)	0	p > 0.999
Ceftriaxone-resistant Infections, no. (%)	0	0	-

Discussion

- The incidence of severe diarrhea was comparable to data in the literature.
- Twelve patients in the pre-intervention arm and ten in the post-intervention arm met criteria for severe diarrhea based on initiation of intravenous fluid support.
- No patients were admitted to the hospital secondary to irinotecan-associated diarrhea.
- The one incident of *C. difficile* infection stemmed from a patient who was started on cefixime, then transitioned to empiric cefepime therapy.

Conclusion

- Implementation of short course cefixime did not increase the incidence of severe diarrhea or result in worse infectious-related outcomes.
- The new schema increased provider adherence and was less burdensome on patients and families.
- This practice change was a safe and effective antimicrobial stewardship initiative that has potential to improve patient quality of life.

Conclusion

- **Limitations:**
  - Retrospective nature
  - Unable to use CTCAE criteria
  - Small sample size
- **Future Directions:**
  - Evaluate toxicities and stewardship outcomes with all courses of irinotecan
  - Better characterize the role of UGT1A1 phenotype on the development of severe diarrhea

Study Team

- **Co-Investigators:**
  - Anthony M. Christensen, PharmD, BCOP
  - Stephen Hall, PharmD
  - Shane J. Cross, PharmD, BCPS
  - Ted Morton, PharmD, BCIDP
  - Melissa S. Bourque, PharmD, BCOP, BCPS
  - Josh Wolf, MBSS, PhD
  - Kristine Crews, PharmD, BCPS
  - Yin Su, MS
  - Li Tang, PhD

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