Spill the Genes! Frequency of high-risk phenotypes and pharmacogenomically actionable medication use in pediatric patients with cancer

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BACKGROUND

- Patients with cancer are frequently prescribed medications with pharmacogenomic actionability.
- Over 95% of patients who have undergone pharmacogenomic testing have at least one reported high-risk result.
- There are few publications that describe the frequencies of pharmacogenomically actionable medication use and high-risk pharmacogenomic phenotypes in pediatric oncology.
- Understanding the prevalence of variant frequencies and the use of pharmacogenomically actionable medications in a real-life cohort of pediatric oncology patients will add to existing literature, guide implementation efforts, and may increase adoption in clinical practice.

PURPOSE

- Describe the overall use of pharmacogenomically actionable medications and frequencies of pharmacogenomic phenotypes in patients with cancer treated at St. Jude Children's Research Hospital (St. Jude).

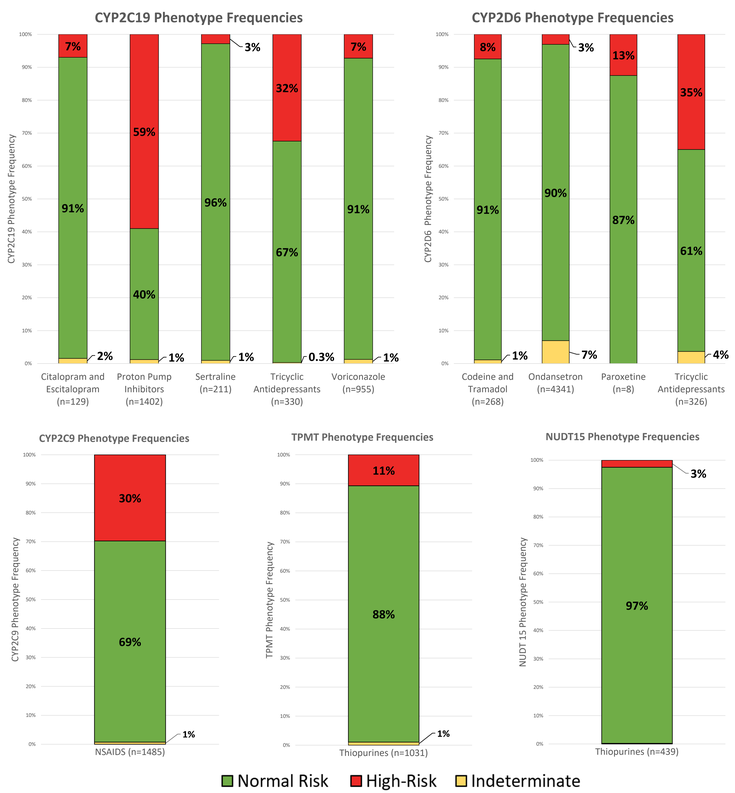
METHODS

- This is a descriptive, cross-sectional study evaluating pharmacogenomic test results and medication use at St. Jude between January 2011 and December 2021.
- Patients at St. Jude are enrolled on the institutional preemptive pharmacogenomic testing protocol, PG4KDS (*www.stjude.org/pg4kds*).
- Pharmacogenes and medications were selected based on frequency of use in the pediatric oncology population and availability of a CPIC guideline.
- Data for 12 pharmacogenes (*CACNA1S, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, G6PD, MT-RNR1, NUDT15, RYR1, TPMT*) and 31 pharmacogenomically actionable medications were assessed.
- Patients who received a pharmacogenomically actionable medication and had a diagnosis of an oncologic disorder were included in the analysis.

RESULTS

Table 1: Patient Demographics and Characteristics (n=7167)

Age, Years (median, range)	7.7 (0.0-51.8)	**Race (patient reported)**	
Gender (patient reported)		American Indian/Alaskan Native	19 (0.3%)
Female	3343 (46.6%)	Asian	152 (2.1%)
Male	3824 (53.4%)	Black	1285 (17.9%)
Genotype Status		Multiple Race	370 (5.2%)
Genotyped	4535 (63.3%)	Native Hawaiian/Pacific Islander	8 (0.1%)
Not Genotyped	2632 (36.7%)	Other	82 (1.1%)
Oncology Diagnosis		Unknown	22 (0.3%)
Leukemia/Lymphoma	2500 (34.9%)	White	5229 (73.0%)
Solid Tumor	2477 (34.5%)	**Ethnicity (patient reported)**	
Brain Tumor	2190 (30.6%)	Hispanic or Latino	939 (13.1%)
		Non-Hispanic or Latino	6153 (85.8%)
		Unknown	75 (1.0%)



Number indicates total (n) of patients who received the medication and were genotyped for the gene of interest

Figure 1: Phenotype Frequencies for Patients Receiving Pharmacogenomically Actionable Medications

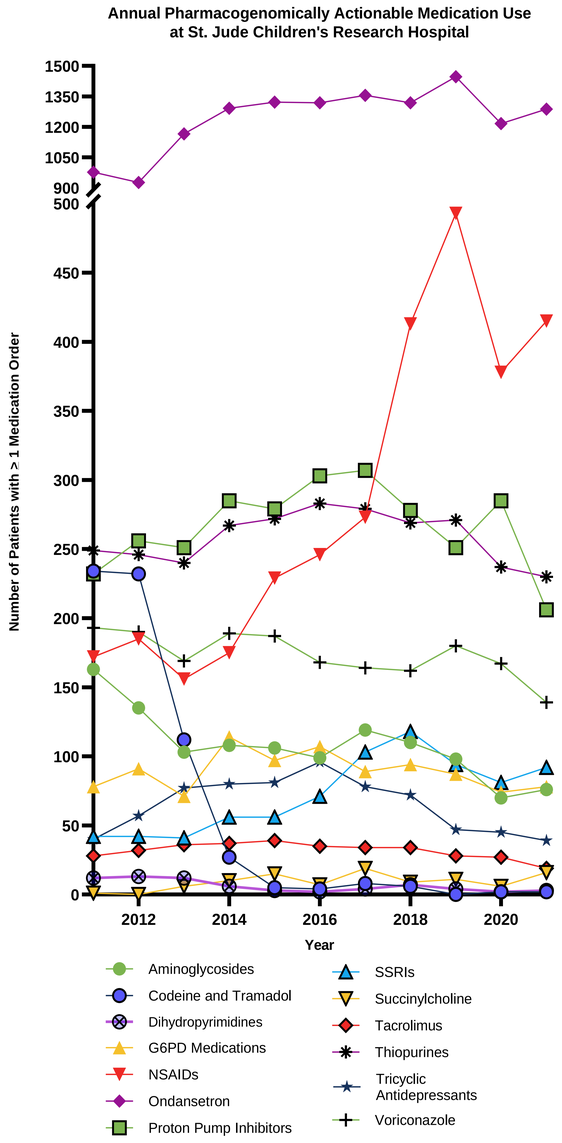


Figure 2: Pharmacogenomically Actionable Medication Use in Pediatric Oncology Patients (2011-2021)

CONCLUSIONS

- Ondansetron, nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), thiopurines, and voriconazole were the most frequently prescribed medications with pharmacogenomic associations.
- The frequency of high-risk phenotypes for *CYP2D6, CYP2C19, CYP2C9, TPMT,* and *NUDT15* ranged from 2% to 59% and varied by medication.
- The widespread use of pharmacogenomically actionable medications and frequency of high-risk alleles supports the implementation of preemptive genotyping in the treatment of pediatric oncology patients.

FUNDING

- Supported, in part, by the National Institutes of Health Cancer Center Support (CORE) grant P30 CA021765 and the American Lebanese Syrian Associated Charities (ALSAC). The funders had no role in study design or preparation of this project.

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MORE INFORMATION

SCAN ME

Supplemental Table 1: Implemented Genes and corresponding medications relevant to oncology patients at St. Jude Children's Research Hospital

Gene	Associated Medications
CACNA1S	Succinylcholine
CYP2B6	Sertraline
CYP2C19	Amitriptyline, Citalopram, Clomipramine, Escitalopram, Imipramine, Lansoprazole, Omeprazole, Pantoprazole, Sertraline, Voriconazole
CYP2C9	Celecoxib, Ibuprofen, Meloxicam
CYP2D6	Amitriptyline, Clomipramine, Codeine, Imipramine, Ondansetron, Paroxetine, Tramadol
CYP3A5	Tacrolimus
DPYD	Capecitabine, Fluorouracil
G6PD	Dapsone, Methylene Blue, Nitrofurantoin, Rasburicase
MT-RNR1	Amikacin, Gentamicin, Tobramycin
NUDT15	Azathioprine, Mercaptopurine, Thioguanine
RYR1	Succinylcholine
TPMT	Azathioprine, Mercaptopurine, Thioguanine

Supplemental Table 2: Drugs and Drug Classes

Line Item	Medications Included
Tricyclic Antidepressants	Amitriptyline, Clomipramine, Imipramine
Proton Pump Inhibitors	Lansoprazole, Omeprazole, Pantoprazole
Aminoglycosides	Amikacin, Gentamicin, Tobramycin
NSAIDS	Celecoxib, Ibuprofen, Meloxicam
Opioid Analgesics	Codeine, Tramadol
Thiopurines	Azathioprine, Mercaptopurine, Thioguanine
Dihydropyridines	Capecitabine, Fluorouracil
SSRIs	Citalopram, Escitalopram, Sertraline, Paroxetine
Ondansetron	Ondansetron
Tacrolimus	Tacrolimus
Dapsone	Dapsone
Methylene Blue	Methylene Blue
Rasburicase	Rasburicase
Nitrofurantoin	Nitrofurantoin
Voriconazole	Voriconazole
Succinylcholine	Succinylcholine

Supplemental Table 3: "High Risk" Phenotype Combination for each Medication

Medication	High-Risk Phenotypes
Amikacin	MT-RNR1 Increased Risk of Aminoglycoside-Induced Ototoxicity
Amitriptyline	CYP2D6 UM, CYP2D6 IM, CYP2D6 PM, CYP2C19 UM, CYP2C19 RM, CYP2C19 PM
Azathioprine	TPMT IM, TPMT PM, NUDT15 IM, NUDT15 PM
Capecitabine	DPYD IM, DPYD PM
Celecoxib	CYP2C9 PM
Citalopram	CYP2C19 UM, CYP2C19 PM
Clomipramine	CYP2D6 UM, CYP2D6 IM, CYP2D6 PM, CYP2C19 UM, CYP2C19 RM, CYP2C19 PM
Codeine	CYP2D6 UM, CYP2D6 PM
Dapsone	G6PD Deficient, G6PD Deficient with CNHSA, G6PD Variable
Escitalopram	CYP2C19 UM, CYP2C19 PM
Fluorouracil	DPYD IM, DPYD PM
Gentamicin	MT-RNR1 Increased Risk of Aminoglycoside-Induced Ototoxicity
Ibuprofen	CYP2C9 PM
Imipramine	CYP2D6 UM, CYP2D6 IM, CYP2D6 PM, CYP2C19 UM, CYP2C19 RM, CYP2C19 PM
Lansoprazole	CYP2C19 UM, CYP2C19 RM, CYP2C19 IM, CYP2C19 PM
Meloxicam	CYP2C9 IM, CYP2C9 PM
Mercaptopurine	TPMT IM, TPMT PM, NUDT15 IM, NUDT15 PM
Methylene Blue	G6PD Deficient, G6PD Deficient with CNHSA, G6PD Variable
Nitrofurantoin	G6PD Deficient, G6PD Deficient with CNHSA, G6PD Variable
Omeprazole	CYP2C19 UM, CYP2C19 RM, CYP2C19 IM, CYP2C19 PM
Ondansetron	CYP2D6 UM
Pantoprazole	CYP2C19 UM, CYP2C19 RM, CYP2C19 IM, CYP2C19 PM
Paroxetine	CYP2D6 UM, CYP2D6 PM
Rasburicase	G6PD Deficient, G6PD Deficient with CNHSA, G6PD Variable
Sertraline	CYP2C19 PM, CYP2B6 PM
Succinylcholine	CACNA1S Malignant Hyperthermia Susceptibility, RYR1 Malignant Hyperthermia Susceptibility
Tacrolimus	CYP3A5 NM, CYP3A5 IM
Thioguanine	TPMT IM, TPMT PM, NUDT15 IM, NUDT15 PM
Tobramycin	MT-RNR1 Increased Risk of Aminoglycoside-Induced Ototoxicity
Tramadol	CYP2D6 UM, CYP2D6 PM
Voriconazole	CYP2C19 UM, CYP2C19 PM