PRECISION: Pharmacogenomics to Enhance Care and Improve Safety in Survivors

Working Groups

CCSS Primary: Genetics
CCSP Primary: Global/Biostatistics/Epidemiology

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Background and Rationale

Over 80% of patients diagnosed with childhood and adolescent cancers will survive their primary disease. There are now over 500,000 survivors of childhood and adolescent cancer, or 1 in 750 people, estimated to live in the United States (1). Even after completion of their cancer treatment, survivors of childhood cancer remain at high risk of morbidity and mortality. Among five-year survivors in the clinically assessed St. Jude Lifetime Cohort Study (SJLIFE), 95% had at least one chronic condition, and 80% had at least one severe chronic condition by age 45 (1). Survivors, especially those with chronic conditions, are at greater risk for polypharmacy and chronic medication use (2, 3). In a national claims database, at three years after the completion of therapy, cancer survivors had higher rates of prescription medication use across numerous medication classes, including opioids, antidepressants, anxiolytics, and antihypertensives than age-, sex-, and region-matched controls (4). In the Childhood Cancer Survivor Study (CCSS), survivors reported a higher number of psychoactive medications, which included analgesics, antidepressants, anxiolytics, and anticonvulsants, than siblings. Risk factors for psychoactive medication use included female sex, radiation, amputation, and recurrence (5). Pediatric cancer survivors also face a higher risk for cardiovascular disease and major adverse cardiovascular events (MACE) compared to age-, race-, and sex-based controls (6). By age 50, the cumulative incidence of a cardiovascular chronic health condition was 93% for survivors of childhood cancer in the SJLIFE cohort (7). In the CCSS, survivors reported using more medications for hypertension, dyslipidemia, or diabetes than siblings (8). Cranial and total body radiation were associated with higher risks of dyslipidemia in SJLIFE (9). Abdominal/pelvic, cranial, and total body radiation, alkylating agents, and sex at birth were associated with higher risks of dyslipidemia in the Dutch Childhood Cancer Survivor (DCCS) LATER 2 study (10).

Pharmacogenomics is the study and application of how germline genetic variations affect the pharmacokinetics and pharmacodynamics of medications to decrease side effects and/or improve efficacy (11). The impact of genetic variation on drug-induced toxicity and efficacy can be significant. For example, clopidogrel, an antiplatelet medication used in the treatment of atherosclerotic cardiovascular disease, is activated by CYP2C19 to an active metabolite that inhibits platelet activity. Patients who have a genetic variation that results in decreased or no CYP2C19 enzyme activity are at higher risk of a recurrent major adverse cardiovascular event (MACE) after a cardiac stent. To maintain similar efficacy, patients who have a CYP2C19 intermediate or poor metabolizer phenotype should be prescribed an alternative anti-platelet agent not metabolized by CYP2C19 (12, 13). Genetic variation in *CYP2C19* and *CYP2D6* can affect the toxicity and efficacy of select antidepressant medications (14). In a pragmatic, randomized controlled trial, a pharmacogenomic-guided approach to prescribing antidepressants resulted in higher depression remission rates than usual care over 24 weeks (15). The use of a multi-gene pharmacogenomics panel reduced the incidence of adverse drug events by 30% in patients who were prescribed medications with pharmacogenomic implications (16).

Preemptive pharmacogenomics occurs when patients are genotyped prior to developing an indication for a medication use (17). The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published clinical practice guidelines for pharmacogenomic-based prescribing for over 100 medications (18). CPIC has categorized over 75 gene-drug pairs as “level A”, for which there is sufficient evidence to recommend a change in prescribing practices based on pharmacogenomic information. An additional 11 gene-drug pairs are categorized as “level B”, which have an optional prescribing recommendation. The CPIC guidelines provide recommendation to tailor pharmacotherapy of many medications commonly prescribed to

survivors of childhood cancer such as antiplatelets, statins, codeine, tramadol, nonsteroidal anti-inflammatory drugs (NSAIDs), atomoxetine, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants.

Multiple population cohorts have shown that over 90% of individuals without cancer history have at least one pharmacogenomic result that may require a change in prescribing to at least one medication (19, 20). However, **the value of pharmacogenomic testing to tailor pharmacotherapy is contingent on the prevalence of prescribed medication use with an actionable pharmacogenomic association in the target population**. A key step toward optimizing medication safety (16), efficacy (12), and adherence (21) with pharmacogenomic information in at-risk populations is to identify specific subpopulations that would benefit from pharmacogenomic testing and to incorporate pharmacogenomic testing into routine clinical care. In 2019, over 15% of pediatric patients enrolled in Medicaid were prescribed a medication with level A CPIC evidence (22). In the *All of Us* cohort, over 20% of adult patients were exposed to a medication with pharmacogenomic-based recommendations for their specific phenotype (19). Key to this proposal, a high prevalence of exposure to medications with an actionable pharmacogenetic association has been demonstrated in patients actively being treated for cancer (23-25). In a Dutch pediatric oncology cohort of over 1100 patients, 16% of patients undergoing active treatment were exposed to a medication with pharmacogenomic prescribing implications with a corresponding actionable phenotype (26). However, little is known regarding the prevalence of exposures to medications that have pharmacogenomic-based prescribing recommendations in survivors of childhood cancer, nor are there data regarding the prevalence of actionable pharmacogenomic variation.

The proposed study will address this knowledge gap and provide essential data to guide pharmacogenomic testing in the childhood cancer survivor population. We hypothesize that survivors of childhood cancer have a high prevalence of exposure to medications with pharmacogenomic-based prescribing recommendations, suggesting potential benefits for pharmacogenomic testing.

Specific aims/objectives/research hypotheses

Aim 1 Determine the prevalence of actionable pharmacogenomic phenotypes as defined by a phenotype with at least one prescribing recommendation for at least one medication by the Clinical Pharmacogenetics Implementation Consortium (CPIC) or Dutch Pharmacogenetics Working Group (DPWG) (Supplemental Table 1) in patients enrolled in St. Jude Life (SJLIFE) and the Childhood Cancer Survivor Study (CCSS) with available genetic data and compare to the general population.

We hypothesize that survivors of childhood cancer will have a prevalence of actionable pharmacogenomic phenotypes similar to the general population without cancer.

Aim 2: Characterize the self-reported use of actionable pharmacogenomic medications defined as medications with prescribing recommendations for pharmacogenomic test results in a CPIC or DPWG guideline in survivors of childhood cancer and compare the prevalence of self-reported use of actionable pharmacogenomic medications in childhood cancer survivors to the general population (e.g., SJLIFE community controls, CCSS siblings).

We hypothesize that a higher proportion of survivors of childhood cancer will be exposed to actionable pharmacogenomic medications than controls.

Aim 2a: *Determine the proportion of survivors who self-report an actionable pharmacogenomic medication and summarize the number of actionable pharmacogenomic medications survivors report.*

Aim 2b: Among those who were prescribed at least one pharmacogenomic medication, calculate the proportion of survivors who have a corresponding actionable phenotype that would have prompted a prescribing recommendation, had the phenotype been known.

Aim 2c: Compare the proportion of survivors who report an actionable pharmacogenomic medication to the proportion of the general population.

Aim 3: Identify cancer-related factors associated with a higher likelihood of receiving an actionable pharmacogenomic medication as a childhood cancer survivor.

We hypothesize that radiation exposure, anthracycline and alkylating agent use, female sex, and history of recurrence will be associated with higher odds of pharmacogenomic medication exposure.

Methods

1. Study Population

Inclusion criteria:

Aim 1: Patients with a history of childhood or adolescent cancer diagnosed enrolled on SJLIFE or CCSS who have whole exome or whole genome sequencing data. Participants who are in both SJLIFE and CCSS will only be counted as SJLIFE participants and excluded from the analysis in CCSS. We will also use SJLIFE community controls with next generation sequencing data available as well as All of Us Research Program participants without a history of cancer.

Aims 2a, 2c, and 3: Patients with a history of childhood or adolescent cancer diagnosed enrolled on SJLIFE or CCSS protocols who have provided at least one completed follow-up survey with information about medication use. Participants who are in both SJLIFE and CCSS will only be counted as SJLIFE participants and excluded from the analysis in CCSS. We will also use SJLIFE community controls and CCSS sibling controls who have provided at least one completed follow-up survey with information about medication use.

Aims 2b: Patients with a history of childhood or adolescent cancer diagnosed enrolled on SJLIFE or CCSS who (1) have whole exome or whole genome sequencing data and(2) provided at least one completed follow-up survey with information about medication use.

Exclusion criteria:

Aim 1: Patients who had an allogeneic transplant prior to next generation sequencing or any history of liver transplant.

Aims 2a, 2c and 3: Any survey of medication use after a liver transplant will be disregarded.

Aim 2b: Patients who had an allogeneic transplant prior to next generation sequencing or any history of liver transplant. In addition, any survey of medication use after a liver transplant will be disregarded.

2. Outcomes(s) of interest

Aim 1: Actionable pharmacogenomic phenotypes are defined as a phenotype with at least one prescribing recommendation in CPIC or DPWG guidelines (see Table 1 for actionable pharmacogenomic phenotypes). Phenotypes will be assigned using the CPIC definitions. Haplotypes will be called using a variety of methods based on the gene. Aldy or Illumina's DRAGEN (Dynamic Read Analysis for Genomics) will be used to call *CYP2D6*. HLA*LA or T1K will be used to call *HLA-A* and *HLA-B*. PharmCAT will be used to call the remaining genes. Of note, *CYP2C19, CYP2D6, CYP3A5, VKORC1,* and *mt-RNR1* cannot be called from whole exome sequencing due to critical intronic variants.

Aim 2 and Aim 3: Actionable pharmacogenomic medications are defined as medications in a CPIC Level A or B gene-drug pair or with a DPWG recommendation (see Table 2).

3. Sociodemographic/Clinical Variables of Interest

- Sex
- Attained age at each survey
- Primary cancer diagnosis
- Age at primary cancer diagnosis (i.e., date of primary cancer diagnosis)
- Reported race/ethnicity
- Date of sample collection from participants with genetic data
- Recurrence of primary cancer and date of diagnosis
- SMN diagnoses and date of diagnosis
- Baseline health insurance status
- Baseline family income level
- Specific cancer treatment exposures of interest (delivered within 5 years of primary cancer diagnosis)
    - Abdominal radiotherapy (RT) (yes/no)
    - Total body irradiation (yes/no)
    - Cranial radiation (yes/no)
    - CSI radiation (yes/no)
    - Chemotherapy (yes/no)
        - Alkylating agents
            - Yes/no and dose as cyclophosphamide-equivalent dose (CED)
            - Specific agents, such as cisplatin, cyclophosphamide, ifosfamide, nitrogen mustard, etc
        - Anthracyclines
            - Yes/No and cumulative dose
        - Methotrexate
            - Yes/No and cumulative dose
        - Etoposide/etoposide phosphate or teniposide
            - Yes/No
    - Surgery for primary disease (yes/no)
        - Limb-sparing

        - Amputation
        - Other
    - Hematopoietic stem cell transplant
    - Health insurance status at surveys with medications
        - Private
        - Medicare/Medicaid
        - Other

4. Analysis

Summary statistics of patient characteristics will be provided including frequencies and proportions for categorical variables and means and standard deviations for continuous variables, stratified by cohort and survivor status. All analyses will be performed in SJLIFE and CCSS and reported separately. If identified associations differ between CCSS and SJLIFE, we will consider CCSS as the primary due to higher numbers of participants and a more frequent survey cadence.

Aim 1: Determine the prevalence of actionable pharmacogenomic phenotypes as defined by a phenotype with at least one prescribing recommendation for at least one medication by the Clinical Pharmacogenetics Implementation Consortium (CPIC) or Dutch Pharmacogenetics Working Group (DPWG) (Supplemental Table 1) in patients enrolled in St. Jude Life (SJLIFE) and the Childhood Cancer Survivor Study (CCSS) with available genetic data and compare to the general population.

We will report the proportions and exact 95% confidence intervals of patients who have at least one actionable pharmacogenomic phenotype and the percentage of patients who have one, two, three, four, and five or more actionable phenotypes. We will report the distribution of phenotypes by primary cancer type We will compare the proportion of survivors with at least one actionable pharmacogenomic phenotype with the proportion of the general population with at least one actionable pharmacogenomic phenotype using a Chi-squared test. We will report CCSS and SJLIFE participants separately. Because WGS is likely to capture more pharmacogenomic phenotypes, we will also report the proportion with or without stratifying type of sequencing (WGS vs. WES).

Aim 2: Characterize the self-reported use of actionable pharmacogenomic medications defined as medications with prescribing recommendations for pharmacogenomic test results in a CPIC or DPWG guideline in survivors of childhood cancer and compare the prevalence of self-reported use of actionable pharmacogenomic medications in childhood cancer survivors to the general population (e.g., SJLIFE community controls, CCSS siblings).

Aim 2a: Determine the proportion of survivors who self-report an actionable pharmacogenomic medication and summarize the number of actionable pharmacogenomic medications survivors report.

We will calculate the proportion of patients who report an actionable pharmacogenomic medication, both overall and stratified by sex, race, and age at the time of the completed survey (e.g., proportion of patients who report an actionable pharmacogenomic medication from ages 18-29, 30-39, 40-49, etc). For survivors who completed multiple questionnaires, if their ages at completion of the surveys fall into several age groups, their responses would be considered in all these the age groups their surveys fall into. If they completed multiple surveys at one age period,

the self-reported medication use across this age period will be combined. We will also calculate the proportions of survivors who report a pharmacogenomic medication by medication class and indication according to the American Hospital Formulary Service (AHFS) classification system (anti-infectives, CNS active medications (psychotherapeutics, analgesics, anticonvulsants, miscellaneous), cardiovascular, antithrombitics, immunosuppressants, antineoplastics, gastrointestinal, and miscellaneous), with or without the same stratification. We will also report the frequency of survivors who report one, two, three, four, or five or more actionable pharmacogenomic medications.

Aim 2b: Among those who were prescribed at least one pharmacogenomic medication, calculate the proportion of survivors who have a corresponding actionable phenotype that would have prompted a prescribing recommendation, had the phenotype been known.

In the subset of survivors who had sequencing data and were prescribed one or more actionable pharmacogenomic medications, we will also calculate the percentage of patients who were exposed to at least one potentially inappropriate actionable pharmacogenomic medication for their corresponding actionable phenotypes. The analysis will be replicated by medication class (e.g., clopidogrel in CYP2C19 intermediate metabolizers and poor metabolizers).

Aim 2c: Compare the proportion of survivors who report an actionable pharmacogenomic medication to the proportion of the general population.

Analysis in Aims 2a and 2b will be replicated in SJLIFE and CCSS controls. To compare between survivors and controls, we will also report the proportion of controls who report use of pharmacogenomic medication by cohort (SJLIFE, CCSS), age brackets, race, and sex. The difference in the proportions between survivors and controls will be compared using logistic regression, adjusting for age at survey completion, race, and sex, stratified by cohort and combined using inverse variance weighting. The number of actionable pharmacogenomic medications prescribed between survivors and controls will also be compared using modified Poisson regression, adjusting for the same covariates. The reason for using logistic or modified Poisson regression instead of mixed-effects models is that SJLIFE controls only completed one survey. We will use data from participants' most recent survey in the regression model. We will also compare the proportion of survivors vs controls who have exposure to a pharmacogenomic medication by indication using the same approach.

Aim 3: Identify cancer-related factors associated with a higher likelihood of receiving an actionable pharmacogenomic medication as a childhood cancer survivor.

To evaluate associations with patients' oncology history and use of an actionable pharmacogenomic medication, we will use unadjusted and adjusted mixed-effects logistic regression. We will use exposure to any pharmacogenomic medication in the past two years at the time of survey completion as the binary outcome. We will test variables associated with their oncology history, including recurrence status, secondary malignancies, treatment modalities, age at primary diagnosis, sex, genomic ancestry, and health insurance status. Preliminary univariable logistic regression models will be performed for each covariate of interest, and covariates with $p<0.2$ will be included in the multivariable model. **Tables and Figures**

Table 1 Baseline cohort demographics

Clinical Characteristics	**SJLIFE survivors**	**CCSS survivors**	**SJLIFE Controls**	**CCSS Sibling Controls**

Age at Primary Diagnosis Median or mean			N/A	N/A
Age at Baseline Survey Mean (SD)				
Age at Last Follow-up Survey Mean (SD)				
Sex				
Male				
Female				
Race				
Ethnicity				
Genomic Ancestry				
Primary Cancer Diagnosis				
Leukemia				
Solid Tumor				
Central Nervous System Malignancy				
Recurrence				
No				
Yes				
Secondary Malignant Neoplasm				
No				
Yes				
Chemotherapy				
No				
Yes				
Alkylating Agents				
No				

Yes				
Anthracyclines				
No				
Yes				
Etoposide or Teniposide				
No				
Yes				
Cranial Radiation				
No				
Yes				
Cranial Spinal Radiation				
No				
Yes				
Abdominal/Pelvic Radiation				
No				
Yes				
Total Body Irradiation				
No				
Yes				
Surgery for primary malignancy				
No				
Amputation				
Limb-sparing				
Other				
Hematopoietic Stem Cell Transplant				
No				
Yes				

Table 2 (Aim 1 and Aim 2: Percentage of patients with actionable pharmacogenomic phenotypes by gene

Gene	Patients with an actionable phenotype (n (%))	Patients with an actionable phenotype reporting a corresponding actionable medication (n %))
ABCG2		
CACNA1S		
CYP2B6		
CYP2C Cluster		
CYP2C19		
CYP2C9		
CYP3A4		
CYP4F2		
CYP2D6		
CYP3A5		
DPYD		
G6PD		
HLA-A		
HLA-B		
MT-RNR1		
NAT2		
NUDT15		
RYR1		
SLCO1B1		
TPMT		
UGT1A1		
VKORC1		

Figure 1 Pie Charts: Percentage of patients with actionable pharmacogenomic phenotypes (No actionable phenotypes, 1 actionable phenotype, 2 actionable phenotypes, 3 actionable phenotypes, 4 or more actionable phenotypes)

(See example below from a previous paper)

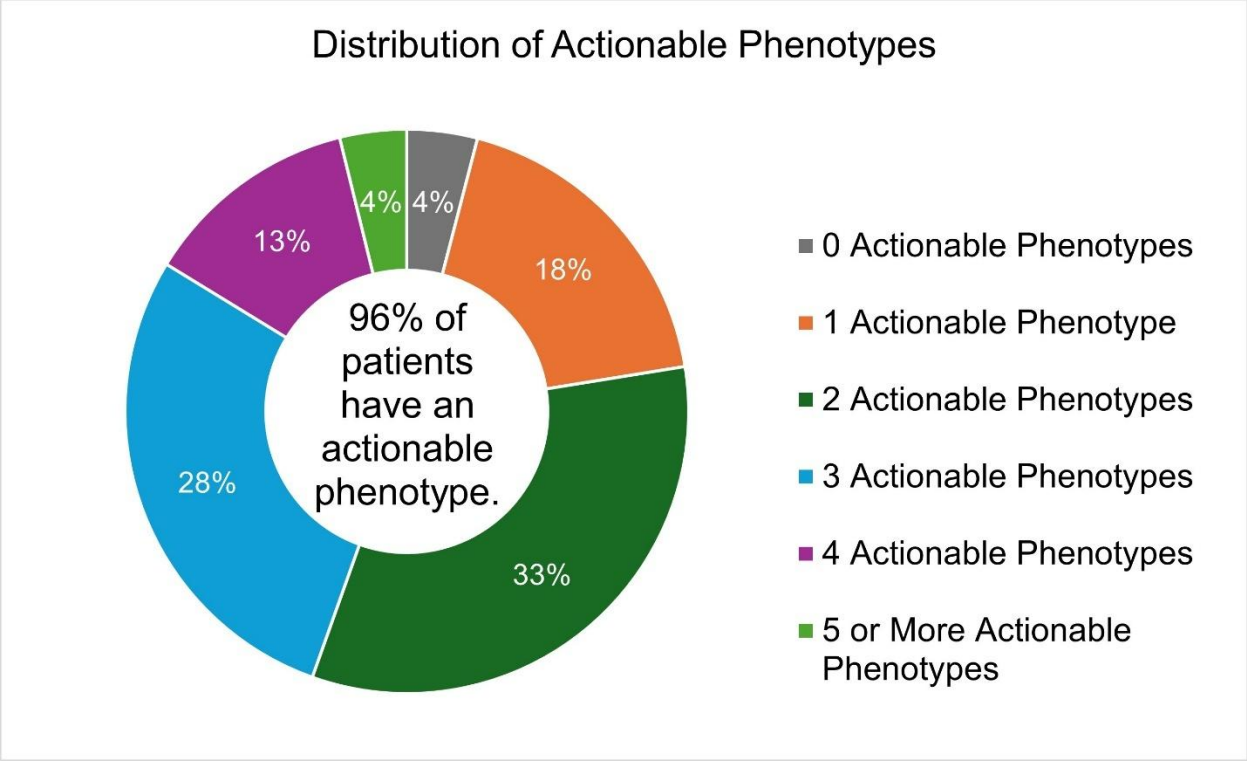


Figure 2 (Aim 2): Percentage of patients who report use of an actionable pharmacogenomic medication by age bracket (A) and time from diagnosis (B) (100% Stacked bar charts, overall and then divided into age brackets and time from diagnosis brackets)

Figure 3 (Aim 2): Percentage of patients with actionable pharmacogenomic medication use by primary diagnosis (leukemia, lymphoma, solid tumor, brain tumor) (Pie Charts)

Figure 4 (Aim 2): Patients who received an actionable pharmacogenomic medication with corresponding actionable phenotype.

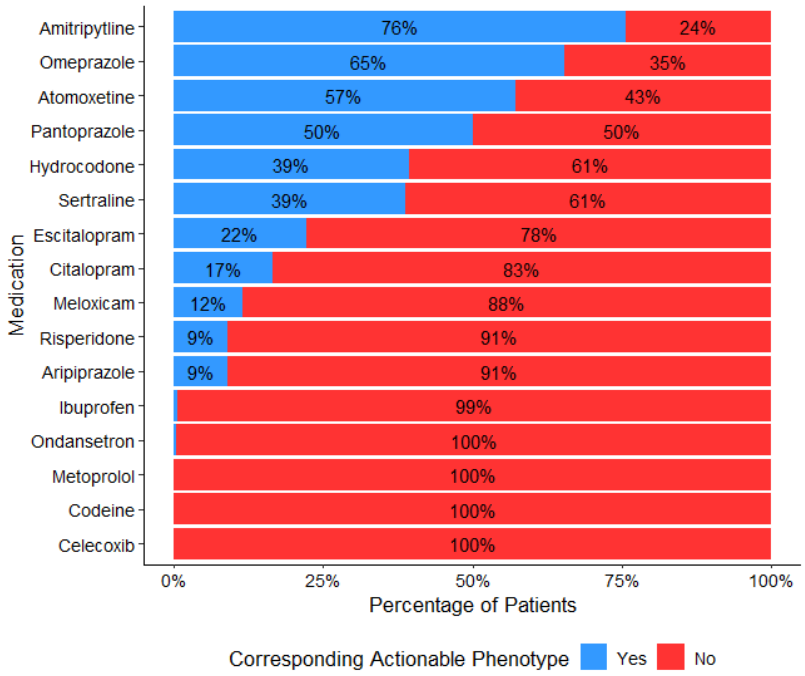


Figure 5 (Aim 2): Comparison of pharmacogenomic medication use in survivors of childhood cancer and in healthy controls by age (100% stacked bar chart, faceted by age brackets with survivors vs control in each age bracket)

Supplemental Table and Figures

Supplemental Table 1 Breakdown of Phenotypes by Gene

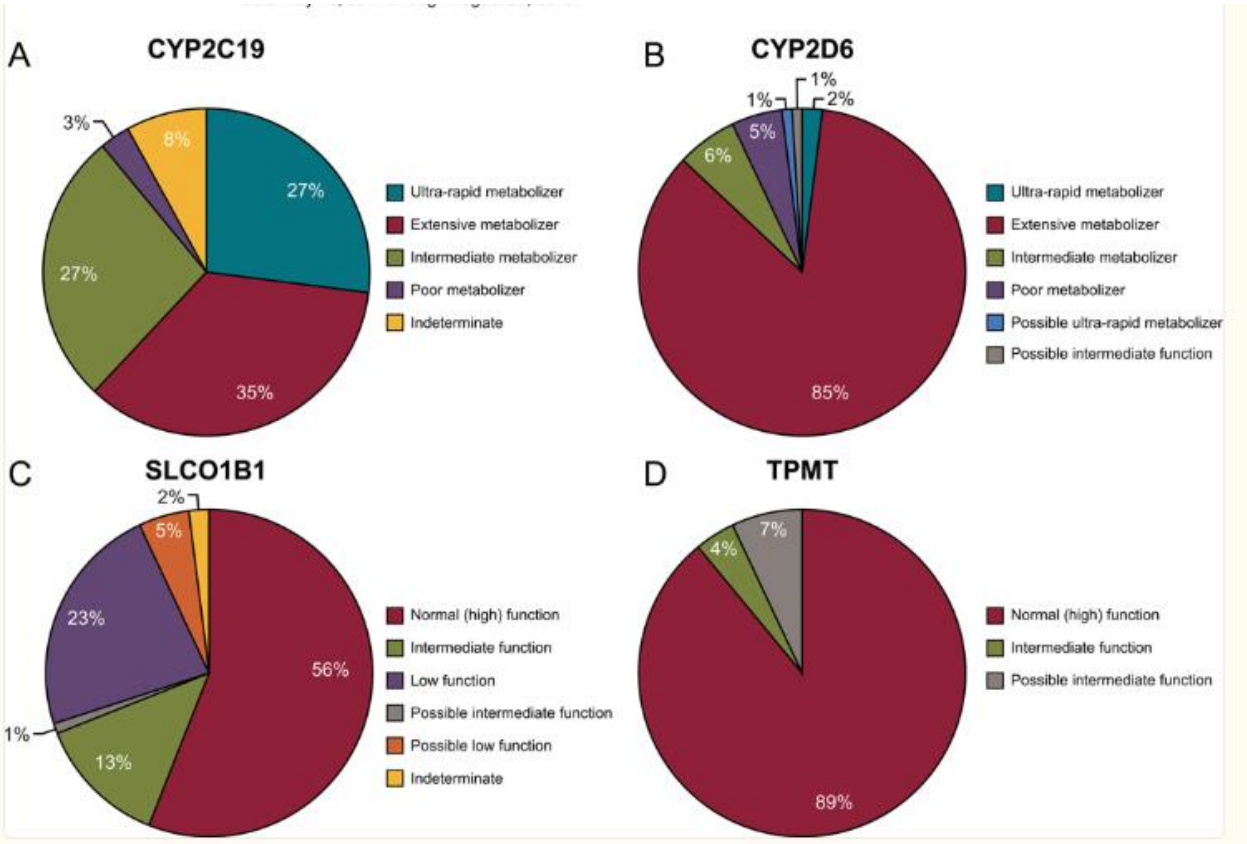
Gene	Phenotype	Patients (n (%))
ABCG2	ABCG2 Normal Function	
	ABCG2 Decreased Function	
	ABCG2 Poor Function*	
CACNA1S	**Malignant Hyperthermia Susceptibility***	
	Uncertain Malignant Hyperthermia Susceptibility	
CYP2B6	CYP2B6 Ultrarapid Metabolizer	
	CYP2B6 Rapid Metabolizer	
	CYP2B6 Normal Metabolizer	
	CYP2B6 Intermediate Metabolizer*	
	CYP2B6 Poor Metabolizer*	
CYP2C Cluster	CYP2C rs12777823 Non-carrier	
	CYP2C rs12777823 Carrier*	
CYP2C19	**CYP2C19 Ultrarapid Metabolizer***	
	CYP2C19 Rapid Metabolizer*	
	CYP2C19 Normal Metabolizer	
	CYP2C19 Intermediate Metabolizer*	

	CYP2C19 Possible Intermediate Metabolizer*	
	CYP2C19 Poor Metabolizer*	
	CYP2C19 Possible Poor Metabolizer*	
CYP2C9	CYP2C9 Normal Metabolizer	
	CYP2C9 Intermediate Metabolizer*	
	CYP2C9 Poor Metabolizer*	
CYP3A4	CYP3A4 Normal Metabolizer	
	CYP3A4 Intermediate Metabolizer	
	CYP3A4 Poor Metabolizer	
CYP4F2	*CYP4F2*3* Non-carrier	
	CYP4F2*3* Carrier	
CYP2D6	**CYP2D6 Ultrarapid Metabolizer***	
	CYP2D6 Normal Metabolizer	
	CYP2D6 Intermediate Metabolizer*	
	CYP2D6 Poor Metabolizer*	
CYP3A5	**CYP3A5 Normal Metabolizer***	
	CYP3A5 Intermediate Metabolizer*	
	CYP3A5 Poor Metabolizer	
DPYD	DPD Normal Metabolizer	
	DPD Intermediate Metabolizer*	
	DPD Poor Metabolizer*	
G6PD	G6PD Normal	
	G6PD Deficient*	
	G6PD Deficient with Chronic Nonspherocytic Hemolytic Anemia (CNSHA)*	
	G6PD Variable*	
HLA-A	*HLA-A*31:01* Negative	
	HLA-A*31:01* Positive	
HLA-B	*HLA-B*15:02* Negative	
	HLA-B*15:02* Positive	
	*HLA-B*57:01* Negative	
	HLA-B*57:01* Positive	
	*HLA-B*58:01* Negative	
	HLA-B*58:01* Positive	
mt-RNR1	**MT-RNR1 Increased Risk of Aminoglycoside-Induced Hearing Loss***	
	MT-RNR1 Uncertain Risk of Aminoglycoside-Induced Hearing Loss	
NAT2	**NAT2 Rapid Metabolizer***	
	NAT2 Intermediate Metabolizer*	
	NAT2 Poor Metabolizer*	
NUDT15	NUDT15 Normal Metabolizer	
	NUDT15 Intermediate Metabolizer*	
	NUDT15 Possible Intermediate Metabolizer*	
	NUDT15 Poor Metabolizer*	
RYR1	**Malignant Hypertherma Susceptibility***	
	Uncertain Malignant Hyperthermia Susceptibility	
SLCO1B1	SLCO1B1 Increased Function	
	SLCO1B1 Normal Function	

	SLCO1B1 Decreased Function*	
	SLCO1B1 Possibly Decreased Function*	
	SLCO1B1 Poor Function*	
TPMT	TPMT Normal Metabolizer	
	TPMT Intermediate Metabolizer*	
	TPMT Possible Intermediate Metabolizer*	
	TPMT Poor Metabolizer*	
UGT1A1	UGT1A1 Normal Metabolizer	
	UGT1A1 Intermediate Metabolizer	
	UGT1A1 Poor Metabolizer*	
VKORC1	*VKORC1-1639 A/A*	
	VKORC1-1639 A/G*	
	VKORC1-1639 G/G*	

*indicates actionable phenotype

Supplemental Figure 1 Breakdown of Phenotype by Gene



Supplemental Table 2 Breakdown of Medication Exposure

Medication	Patients Who Received the Medication (n)	Patients With a Corresponding Phenotype in EHR (n)	Patients with a Corresponding *Actionable* Phenotype (n (%))
Ondansetron			
Ibuprofen			
Escitalopram			
Sertraline			
Omeprazole			
Meloxicam			
Hydrocodone			
Amitriptyline			
Oxcarbazepine			
Pantoprazole			
Citalopram			
Atomoxetine			
Metoprolol			

The results of this study will demonstrate that survivors are childhood cancer will likely benefit from pharmacogenomic testing due to a high frequency of actionable pharmacogenomic phenotypes and medications. This is a population at risk for many chronic conditions that may require pharmacotherapy, and pharmacogenomic testing may help tailor therapy to improve outcomes and minimize toxicity. The results of this study will be used to guide the implementation of pharmacogenomics through clinical trials in this population.

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