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Frequency and Implications of High-Risk Pharmacogenomic Phenotypes Identified in a Diverse Australian Pediatric Oncology Cohort

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ABSTRACT

Pharmacogenomics remains underutilized in pediatric oncology, despite the existence of evidence-based guidelines. Implementation of pharmacogenomics-informed prescribing could improve medication safety and efficacy in pediatric oncology patients, who are at high risk of adverse drug reactions. This study examines the prevalence of high-risk pharmacogenomic phenotypes and the prescription of relevant medications in a diverse Australian pediatric oncology cohort, highlighting the potential impact of pharmacogenomic testing in this unique population. Whole genome sequencing data from 180 patients were analyzed to assess 14 genes with evidence-based pharmacogenomic guidelines relevant to pediatric oncology. Over 90% of patients had at least one high-risk phenotype, with 20% presenting four or more. Ondansetron, mercaptopurine, omeprazole, pantoprazole, and voriconazole were commonly prescribed medications that have pharmacogenomic prescribing recommendations, with the latter three showing the highest actionability rates. High-risk phenotypes were most frequently observed for *CYP2C19* and *CYP2D6*, with 30% of patients having a high-risk phenotype for both genes. This study underscores the potential utility of pharmacogenomics in pediatric oncology patients across a range of pharmacogenes and commonly prescribed medications. The findings support advocacy for implementing broad, pre-emptive pharmacogenomic testing in oncology patients to improve treatment safety and efficacy.

JEL Classification: DEI

Summary

- What is the current knowledge on the topic?
  - Evidence based guidelines for pharmacogenomic (PGx) informed prescribing have not been widely implemented in pediatric oncology despite the inclusion of many commonly prescribed supportive care medications. Population PGx phenotype frequencies have been used to predict the utility of these prescribing recommendations, yet these estimates are largely based on homogeneous populations. In contrast, Australia's population is ancestrally diverse and to date, the potential utility of PGx testing in an Australian pediatric oncology cohort remains unexplored.
- What question did this study address?
  - This study investigated the utility of broad, pre-emptive PGx testing in Australian pediatric oncology patients, with a focus on supportive care medications.
- What does this study add to our knowledge?
  - This study reports the prevalence of high-risk PGx phenotypes for 14 genes relevant to commonly prescribed pediatric oncology medications. 90% of patients were found to have high-risk phenotypes, and significant actionability rates were observed for omeprazole, pantoprazole, voriconazole, and sertraline. High-risk phenotypes were most frequently identified for *CYP2C19* and *CYP2D6*, with 30% of patients having a high-risk phenotype for both genes.
- How might this change clinical pharmacology or translational science?
  - The study findings strongly support the implementation of broad, pre-emptive pharmacogenomic testing in Australian oncology patients to improve treatment safety and efficacy. Additionally, they provide a framework for future studies aimed at improving medication response prediction models and advancing personalized medicine.

1 | Introduction

The survival outcomes for pediatric oncology patients have considerably improved over time, with 5-year overall survival rates now exceeding 80% [1, 2]. However, treatment-related toxicities can be severe, debilitating, and even life-threatening [1]. Efforts are being made to enhance prediction, prevention, and treatment of toxicities, aiming to improve the quality of life of cancer survivors [1, 2]. One approach to reducing toxicities is the use of genomic information to guide medication prescribing, known as pharmacogenomics (PGx) [3]. PGx can be used to guide treatment with chemotherapeutic agents, such as thiopurine dosing informed by *TPMT/NUDT15* genotypes/phenotypes, as well as influence the choice and dose of supportive care medications such as ondansetron [4, 5]. In addition to reducing toxicity, implementing PGx guidelines can also improve medication efficacy [5–7].

Despite the existence of international, evidence-based PGx guidelines from organizations such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) [4, 8, 9], PGx remains widely underutilized in clinical pediatric oncology settings. Only one PGx guideline has been incorporated into pediatric standard of care in Australia—TPMT/NUDT15 guided prescribing for thiopurines in patients with lymphoblastic leukemia [4]. Yet there are additional CPIC guidelines available for multiple medications commonly used in pediatric oncology supportive care that have not been implemented, such as omeprazole, voriconazole, and ondansetron [5, 7, 10]. The utility of implementing these guidelines has been investigated in adult cohorts, where pre-emptive pharmacogenomic testing has demonstrated a significant reduction in adverse drug reactions [11]. Whilst these results have not yet been replicated in a pediatric oncology cohort, PGx has the potential to improve treatment outcomes through predicting both safety and efficacy.

The frequency of specific genetic mutations can vary between populations, which can translate into variations in the resulting phenotypes [12]. Therefore, some populations may be at higher risk of altered metabolism of specific medications. Australia has one of the most diverse populations in the world, with residents identifying with over 300 ancestries [13]. This diversity presents challenges in predicting the frequency of at-risk phenotypes and which gene-drug pairs to prioritize for PGx testing. This study aims to determine the prevalence of high-risk PGx phenotypes in an Australian pediatric oncology cohort of 180 patients. The findings provide insight into the most important genes to assess and the most frequently affected medications used in pediatric oncology, potentially guiding personalized treatment strategies in Australia.

2 | Methods

2.1 | Study Design and Population

This is an observational cohort study of PGx results obtained from patients enrolled in the broader Australian PGx implementation study "Minimising Adverse Drug Reactions and Verifying Economic Legitimacy – Pharmacogenomic Implementation in Children (MARVEL-PIC)" [14]. The MARVEL-PIC study received ethical approval (RCH HREC 89083), and in accordance with this approval and the principles outlined in Australian research standards, this study obtained written informed consent from adolescent and young adult patients who are deemed mature and capable, as well as from their parents or guardians [14]. Where minors were considered not mature and capable, written consent was obtained from parents or guardians. Consenting study team members conducted initial eligibility discussions with clinicians prior to approaching potential participants. Written information statements were provided to young adult and adolescent participants and their parents or guardians for review for at least 24 h before consent forms were signed. Where appropriate and feasible, both the participant and their parents or guardians were included in the consent process. Full details of the study are available in the published protocol [14]. One hundred and eighty pediatric oncology patients recruited between February 2023 and December 2024 at The Royal Children's Hospital, Melbourne, were included in this sub-study and their whole genome sequencing (WGS) data analyzed. Patient electronic medical records were accessed at four timepoints over a

12-week period, as part of the MARVEL-PIC study [14]. Study data were collected and managed using REDCap electronic data capture tools [15]. Ancestry data was self-reported, with patients given seven broad pre-colonization biogeographical groups used by Pharmacogenomics Knowledgebase (PharmGKB) to annotate PGx studies [16]. Patients could choose up to two ancestral groups.

For the purposes of this study, we defined "high-risk" PGx variants as identified variants for which there are existing international prescribing recommendations for alternate dosing, avoidance, or additional monitoring of a medication. A variant becomes "actionable" when a corresponding medication has been prescribed to a patient with a "high-risk" variant.

2.2 | Pharmacogene-Drug Pair Selection

CPIC and DPWG pharmacogene (gene that influences medication pharmacokinetics or pharmacodynamics) and drug guidelines were assessed for their relevance to pediatric oncology [5, 8, 17, 18]. Guidelines were selected for inclusion in this study based on prescribing frequency and potential to avoid harm. With the exception of *CYP2B6*, all pharmacogene-drug pairs in this study were classified as CPIC Level A (the CPIC guideline contains at least one recommended prescribing action). We decided to include *CYP2B6* (Level B) as results impact the guideline recommendations for *CYP2C19*/sertraline (Level A). *UGT1A1*/irinotecan, *ABCG2*/allopurinol, and *HLA-B*57:01*/flucloxacillin guidelines were taken from the DPWG and were assigned DPWG Level 1A evidence. Gene-drug pairs are shown in Table 1.

TABLE 1 | Gene-drug pairs investigated in this study.

Gene	Drug
ABCG2	Allopurinol
CYP2B6	Sertraline
CYP2C19	Amitriptyline, Citalopram, Omeprazole, Pantoprazole, Sertraline, Voriconazole
CYP2D6	Amitriptyline, Codeine, Nortriptyline, Flecainide, Fluvoxamine, Tramadol, Paroxetine, Ondansetron, Tropisetron
CYP3A5	Tacrolimus
DPYD	Fluorouracil, Capecitabine
G6PD	Rasburicase, Methylene blue
*HLA-A*31:01*	Carbamazepine
*HLA-B*58:01*	Allopurinol
*HLA-B*15:02*	Carbamazepine, Oxcarbazepine
*HLA-B*57:01*	Flucloxacillin
MT-RNR1	Amikacin
m.1555A>G	
m.1494C>T	
m.1095T>C	
NUDT15	Azathioprine, Mercaptopurine, Tioguanine
SLCO1B1	Simvastatin
TPMT	Azathioprine, Mercaptopurine, Tioguanine
UGT1A1	Irinotecan

2.3 | Whole Genome Sequencing Data Analysis

DNA was purified using the QIAsymphony DNA Mini Kit, followed by DNA preparation using the Illumina DNA PCR-Free Prep. WGS was performed on an Illumina NovaSeq X, generating 2×150 base pair reads, which were aligned to the GRCh38 reference genome using DRAGEN (Illumina) targeting a depth of at least 27×. An in-house PGx pipeline was used for genotyping, which went through updates over the analysis period to remain current. Initially, the pipeline included HLA-HD (*HLA-A* and *HLA-B* genotyping), GATK HaplotypeCaller (*ABCG2* only), Mitoreport (*MT-RNR1* only), Cyrius v1.1.1 (*CYP2D6* only), and Aldy v4.4 and Stargazer v1.0.8 for the other genes, including *CYP2D6* [19–24]. However, as not all tools supported the GRCh38 reference genome, sequencing reads initially were realigned to GRCh37. With the transition to GRCh38, Stargazer was updated to v2.0.3, Aldy to its latest version, StellarPGx v1.2.7 was added to the pipeline as an additional tool. Later, Cyrius was replaced with BCyrius [25]. In all cases, except for *HLA*s, *ABCG2* and *MT-RNR1*, a genotyping call was made when at least two tools reached a consensus on the diplotype. This approach has previously been demonstrated to have a high concordance with the ground truth and a high call rate [26]. *HLA-A* and *HLA-B* were determined only with HLA-HD from unaligned reads. The latest CPIC diplotype-to-phenotype translation tables (available at https://cpicpgx.org) at the time of analysis were used to infer the predicted phenotype from the consensus diplotype. For *CYP2D6*, CPIC allele functionality references were used to calculate the activity score for each diplotype. *CYP2D6* phenotypic groups are linked to activity scores (AS) as follows: poor metabolizers (AS = 0), intermediate metabolizers (AS = 0.25–1), normal metabolizers (AS = 1.25–2.25) and ultrarapid metabolizers (AS > 2.25) [9]. In one case for *CYP2C19*, a "Likely Poor Metabolizer" (*2/*9) was grouped into the "Poor Metabolizer" group.

Regarding *UGT1A1*, due to the challenges tools have in genotyping the gene and their inability to provide consensus results in most cases, the method was revised and consequently, testing was limited to *6, *27, *28, *37, and *80. Additionally, for consensus purposes, calls of *80 + *28 were simplified to *28, as *28 is a decreased-function allele with or without *80. *CYP2B6* was added to the list of targeted genes at a later stage. As a result, the number of patients genotyped for *UGT1A1* and *CYP2B6* is lower than for others.

The final results were processed using R v4.3.3 [27] to calculate the outcomes and figures. For the calculation of high-risk phenotypes, all phenotypes with decreased or increased activity were considered high risk. This also included any relevant HLA phenotypes (*HLA-A* *31:01 positive, and *HLA-B* *15:02, *57:01 and *58:01 positive) as well as three *MT-RNR1* variants (m.1095T>C, m.1494C>T and m.1555A>G). Phenotypes

classified as "indeterminate" due to the presence of one or two haplotypes with unknown or uncertain functionality were not considered high-risk; instead, they were categorized as "unknown". Additionally, the *G6PD* phenotype "variable" in heterozygous females was categorized as "unknown" as the exact function cannot be predicted solely from the genotype [28].

2.4 | CYP2D6 Phenoconversion Calculator

To estimate the incidence of CYP2D6 phenoconversion in this cohort, a calculator tool designed to standardize the integration of phenoconversion into practice was used [29]. This calculator is based on an algorithm that requires the initial calculation of the CYP2D6 genotype activity score, multiplication of the activity score by 0.5 if a moderate CYP2D6 inhibitor is also being taken and by 0 if a strong CYP2D6 inhibitor is being taken [29]. This final activity score is then converted to a predicted phenotype, which is compared with the initial phenotype to ascertain whether phenoconversion has occurred [29].

3 | Results

3.1 | Patient Characteristics

The 180 patients were between 0 and 18 years of age, 55.6% male and 44.4% female. Ancestry was self-reported, and patients were able to choose up to two ancestral categories. Most patients identified as European (53.3%) or Oceanian (30.6%), from the Oceanian cohort, only small numbers identified as Aboriginal (2.8%) or Maori (1.7%) and thus a limited proportion reflected pre-colonial groups. The majority of patients were diagnosed with Acute Lymphoblastic Leukemia/Lymphoma (B-cell or T-cell). Further patient characteristics are outlined in Table 2.

3.2 | Patients With High-Risk Phenotypes

High-risk phenotypes were determined from the dataset based on genotyping calls where a consensus was achieved, if required. No consensus among tools was observed in some cases across the genes analyzed with multiple tools, with the highest frequencies occurring for *DPYD* (16.1%), *SLCO1B1* (8.89%) and *UGT1A1* (8.16%), while lower frequencies were noted for *CYP2B6* (3.57%), *CYP2C19* (1.67%) and *CYP2D6* (1.11%). For *CYP3A5*, *G6PD*, *NUDT15*, and *TPMT*, all results were consensus. Results for *UGT1A1* and *CYP2B6* are based on 49 and 56 genotyping calls, respectively.

The highest frequency of high-risk phenotypes was detected for *CYP2C19*, with almost a third of patients designated as poor/intermediate metabolizers and another third as rapid/ultrarapid metabolizers (Figures 1 and 2A). This was followed by *UGT1A1*, with approximately 40% of patients assigned as intermediate metabolizers. Almost half of the patients had a high-risk phenotype for *CYP2D6* (mostly intermediate/poor metabolizers), and reduced *ABCG2* function was identified in a quarter of the

TABLE 2 | Patient characteristics table.

	Total patients $n = 180$ (%)
Sex	
Male	100 (55.6%)
Female	80 (44.4%)
Self-reported ancestry	
American	5 (2.8%)
East Asian	22 (12.2%)
European	96 (53.3%)
Central/South Asian	24 (13.3%)
Near Eastern	9 (5%)
Oceanian	55 (30.6%)
Aboriginal	5 (2.8%)
Maori	3 (1.7%)
Sub-Saharan African	10 (5.6%)
Missing	15 (8.3%)
Unsure	6 (3.3%)
Diagnosis:	
Aplastic anemia (SAA)	8 (4.4%)
Anaplastic Large Cell Lymphoma	3 (1.7%)
ALL B Cell	41 (22.8%)
ALL T Cell	16 (8.9%)
Acute Promyelocytic Leukemia (APML)	1 (0.6%)
Acute Myeloid Leukemia (AML)	10 (5.6%)
Atypical Teratoid Rhabdoid Tumor (ATRT)	1 (0.6%)
Ewing's Sarcoma (ES)	7 (3.9%)
Ependymal Tumor (ET)	1 (0.6%)
Germ Cell Tumor (GCT)	4 (2.2%)
Hepatoblastoma (HBT)	4 (2.2%)
Hodgkin's Lymphoma (HL)	14 (7.8%)
Haemophagocytic Lymphohistiocytosis (HLH)	1 (0.6%)
Inborn Errors of Metabolism (IEM)	3 (1.7%)
Langerhan's Cell Histiocytosis (LCH)	3 (1.7%)
Low Grade Glioma (LGG)	8 (4.4%)
Medulloblastoma (MBL)	4 (2.2%)
Myelodysplastic Syndrome (MDS)	1 (0.6%)
Neuroblastoma (NBL)	6 (3.3%)

(Continues)

TABLE 2 | (Continued)

	Total patients $n = 180$ (%)
Non-Hodgkin's Lymphoma (NHL)	9 (5%)
Osteosarcoma (OS)	11 (6.1%)
Primary Immunodeficiency (PID)	2 (1.1%)
Retinoblastoma (RBL)	3 (1.7%)
Rhabdomyosarcoma (RMS)	7 (3.9%)
Synovial Sarcoma (SS)	1 (0.6%)
Wilm's Tumor (WT)	9 (5%)
Miscellaneous	2 (1.1%)

cohort. There were no high-risk phenotypes for either *MT-RNR1* or *G6PD* (where one "variable" phenotype was considered as "unknown") and each of the *HLA-A* and *HLA-B* variants were detected in < 10% of the individuals. Overall, more than 90% of patients had at least one high-risk phenotype, while 20% carried four or more and only 6.7% had none (Figure 2B).

Patients were additionally analyzed according to *CYP2D6* diplotype activity scores (AS) (Figure 3). Nearly half were classified as normal metabolizers, with an AS of 2.0 being the most common (32.8%), followed by 1.25 (16.1%). Intermediate metabolizers comprised 38.4% of all patients, including 21.8% with an AS of 1.0. AS 1.0 and 1.25 were the second and third most common scores, with a small difference between them, yet they fall into different phenotype brackets. A small proportion (8%) had activity scores of 0 or 0.25, yet these activity scores are also in different phenotype brackets.

3.3 | Pediatric Oncology Medications With PGx Prescribing Recommendations

Through medication histories, we determined that a vast majority of patients in this study were prescribed ondansetron (87.8%), and a significant number were prescribed omeprazole (38.3%), mercaptopurine (23.3%), pantoprazole (18.9%) and voriconazole (15%). Frequencies of patients prescribed PGx medications are found in Table 3. PGx actionability rates were highest amongst patients taking omeprazole (39.1%), voriconazole (44.4%) and sertraline (40%), when analyzed as a proportion of patients prescribed the PGx medication.

3.4 | Utility of a Combinatorial Approach to PGx Testing in Pediatric Oncology Patients With Leukemia/Lymphoma

Frequencies of high-risk phenotype combinations were analyzed to identify trends within our patient cohort (Figure 4). 57% of patients had a high-risk *CYP2C19* phenotype in combination with another high-risk phenotype for a pharmacogene interrogated in this study. 48% had a high-risk *CYP2D6* phenotype in combination with another high-risk phenotype. 30% of patients had high-risk phenotypes for *CYP2C19* and *CYP2D6*, and 9% of total patients had high-risk phenotypes for *CYP2C19*, *CYP2D6*, and *ABCG2*.

3.5 | Estimating Occurrence of Phenoconversion

Phenoconversion (a mismatch in observed gene phenotype and the predicted genotype-inferred phenotype) can occur due to concomitant medications or comorbidities and affect the accuracy of genotype predicted phenotypes [30]. The number of patients in this cohort taking a known CYP inhibitor or inducer, which may affect PGx results, was recorded. There is also evidence that phenoconversion can occur with TPMT, UGT1A1, TPMT, and SLCO1B1; however, these drug-gene interactions are less well characterized [31].

Five patients (2.8% overall) who were predicted to be a normal or intermediate CYP2D6 metabolizers based on genotype were prescribed a **strong CYP2D6 inhibitor** (terbinafine $n = 1$, fluoxetine $n = 4$). Using a CYP2D6 phenoconversion calculator [29], all of these patients were classified as CYP2D6 poor metabolizers due to drug-induced phenoconversion. Whilst the assessment of medication-induced CYP2C19 phenoconversion in a clinical setting has been less studied than CYP2D6 phenoconversion [32], it is known that fluoxetine, probenecid, omeprazole, and voriconazole are all **CYP2C19 inhibitors** with the potential to cause phenoconversion [30, 32]. In our cohort, a significant number (57%) of patients were prescribed medications that could potentially affect their CYP2C19 genotype-inferred phenotype: fluoxetine ($n = 4$), probenecid ($n = 1$), omeprazole ($n = 69$), fluconazole ($n = 21$), voriconazole ($n = 27$).

4 | Discussion

This study reported phenotype frequencies of 14 pharmacogenes relevant to pediatric oncology in a diverse, Australian cohort. We identified high-risk PGx phenotypes in more than 90% of our patients, which is in keeping with other PGx cohort studies that have reported 80%–100% depending on the number and type of genes interrogated [33, 34]. Given that pediatric oncology patients are often prescribed multiple medications, many of them with PGx prescribing recommendations, this study highlights the role of PGx in optimizing therapy. The medications that had the highest actionability rates were all supportive care medications, due to the combination of frequency of prescription and prevalence of high-risk phenotypes for those metabolizing genes. The impact of identified pharmacogene-drug pairs can be considered according to frequency of actionability, in addition to potential for harm.

4.1 | High Potential for Actionability: *CYP2C19* and *CYP2D6*

CYP2C19 had the greatest proportion of high-risk phenotypes from genes interrogated. This has implications for patients prescribed omeprazole and pantoprazole (proton pump inhibitors used for ulcers, reflux and gut-protection), voriconazole (a first-line

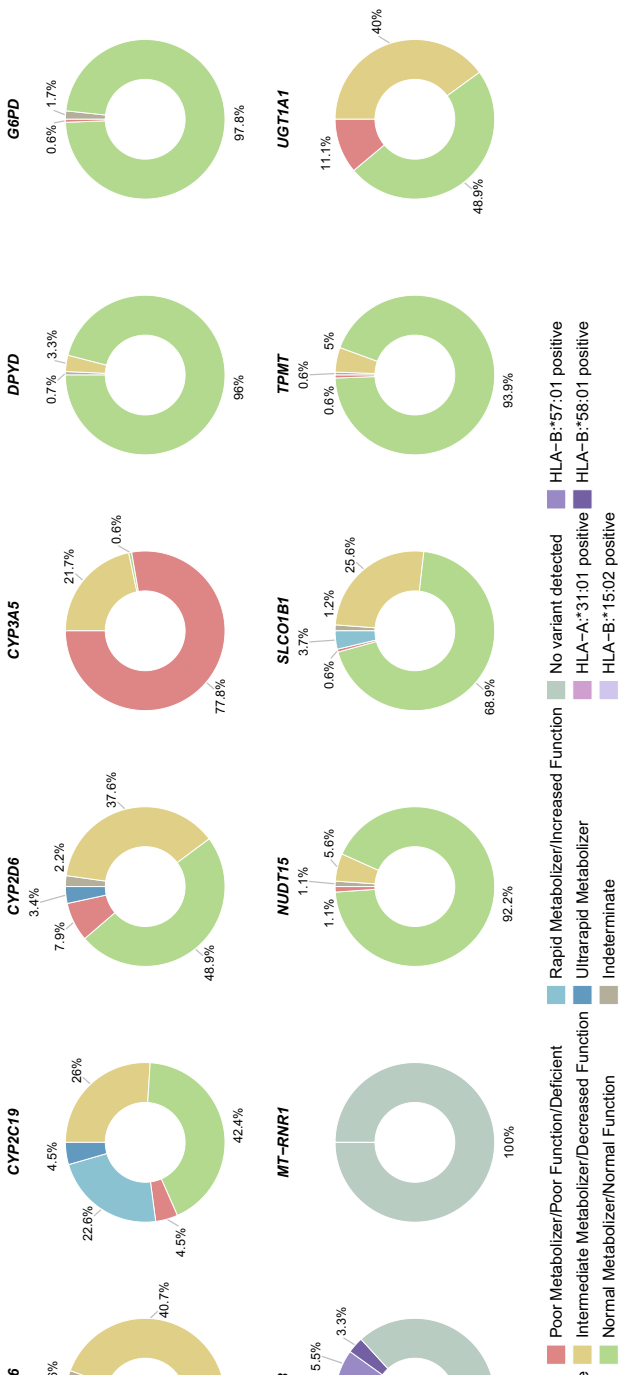

FIGURE 1 | Phenotype frequencies observed in the cohort for each gene.

antifungal agent) and sertraline (selective serotonin reuptake inhibitor antidepressant). These supportive care medications carried high actionability rates, and omeprazole, pantoprazole, and voriconazole were all commonly prescribed in this cohort.

The *CYP2D6* gene is highly polymorphic, with variations in the gene resulting in changes to enzyme activity and a known spectrum of enzyme activity amongst individuals [5]. We found that nearly half of the study participants had a high-risk CYP2D6 phenotype, which impacts patients prescribed tramadol (an opioid analgesic) and ondansetron (5-HT_3 receptor antagonist first-line antiemetic), which was prescribed to 88% of patients. However, due to a lack of evidence, current prescribing guidelines for ondansetron only make alternative recommendations for ultrarapid metabolizers, who comprise just 3.5% of our cohort [5]. This restricts ondansetron recommendations for CYP2D6 non-normal metabolisers.

We also reported frequencies of *CYP2D6* activity scores, as calculated using consensus recommendations for standardized *CYP2D6* genotype to phenotype translation [9]. 38% of patients had activity scores of 1.0 (22.%) and 1.25 (16.%). This cluster demonstrates the complexity of the *CYP2D6* genotype to phenotype translation. An activity score of 1 translates to an intermediate metabolizer, yet 1.25 is classified as a normal metabolizer according to the consensus guidelines [9]. A translation system that reflects the *CYP2D6* activity score continuum rather than categorizing into four phenotypes has previously been suggested, and the distribution of our results may support this approach [35].

4.2 | Moderate Potential for Actionability: *CYP3A5* and *ABCG2*

Whilst 22% of patients had a high-risk phenotype for *CYP3A5*, tacrolimus was less frequently prescribed, corresponding to low actionability. However, recommendations to prescribe 1.5–2 times the recommended starting dose for patients who are normal or intermediate metabolizers are critical, given that higher tacrolimus levels have been shown to reduce post-transplant infections, acute graft-versus-host disease, and other transplant-related complications [6, 36].

Around a quarter of patients carried high-risk *ABCG2* phenotypes, which may require higher doses of allopurinol due to reduced uric acid excretion as recommended by the DPWG [18]. The ability to determine *ABCG2* phenotype could significantly impact the clinical care of the 22% of patients prescribed allopurinol, providing results could be returned in a timely fashion. However, it is also necessary to determine whether the HLA-B:*58:01 variant is present in patients prior to adopting recommendations to increase the allopurinol dose.

4.3 | Lower Actionability but Increased Severity Adverse Drug Reactions: *MT-RNR1*, *HLA-A*, and *HLA-B*

None of the participants had a high-risk *MT-RNR1* phenotype. Whilst infrequently occurring (<1.8%), specific variants of *MT-RNR1* have been associated with permanent

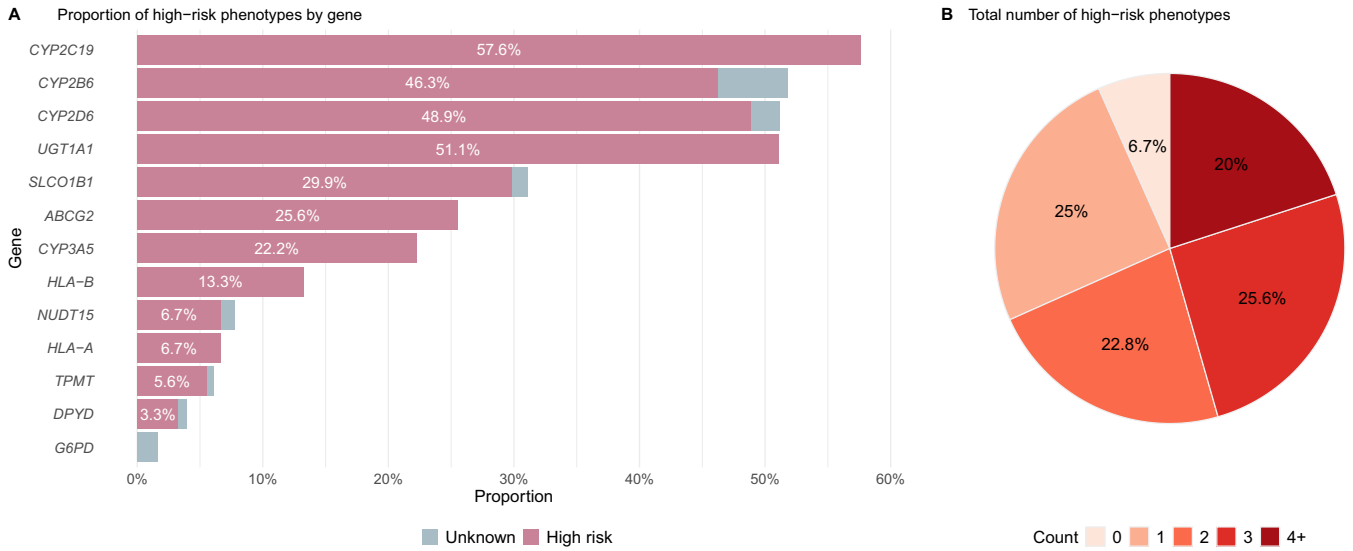

FIGURE 2 | Proportion of high-risk phenotypes by gene (A) and total number of high-risk phenotypes (B).

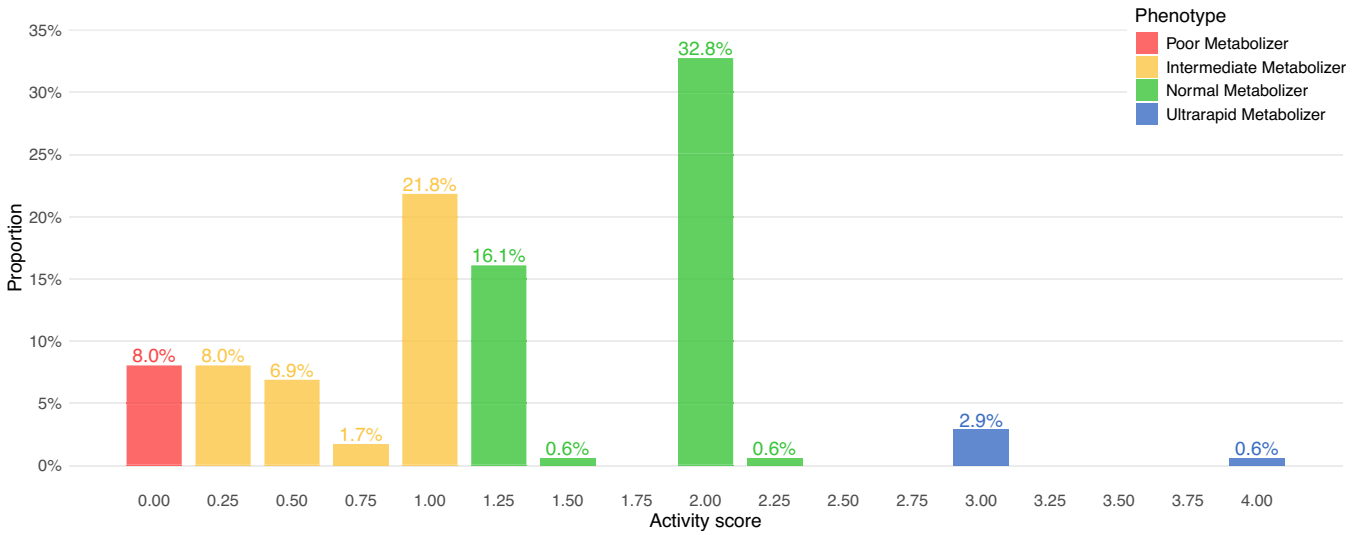

FIGURE 3 | *CYP2D6* activity score distribution in the cohort.

aminoglycoside-induced hearing loss, and recommendations are to avoid amikacin in these patients unless there is a lack of safe or effective alternative therapies [37]. Given that 5% of patients were prescribed amikacin (likely to be an underestimation) the *MT-RNR1* phenotype remains of high clinical significance in this patient cohort. Medications linked to cutaneous adverse reactions in patients with specific *HLA-A* and *HLA-B* variants include carbamazepine, oxcarbazepine, and allopurinol. Whilst allopurinol is used frequently in patients with acute leukemias/lymphomas, carbamazepine and oxcarbazepine are less often prescribed. However, these pharmacogene-drug pairs are still considered significant due to the potential severity of the cutaneous adverse reactions.

4.4 | Chemotherapy

TPMT/NUDT15, *UGT1A1*, and *DPYD* genotype can and should be used to guide chemotherapy prescribing. There is sufficient evidence to support international prescribing recommendations for these genes in relation to thiopurines, irinotecan, and fluoropyrimidines, and they have been widely adopted in clinical practice [4, 38, 39].

Almost all patients carried a high-risk phenotype and notably, 20% of patients had four or more high-risk phenotypes. While single, targeted pharmacogenetic results are useful, it is more important to consider the implications of high-risk phenotypes across the breadth of supportive care medications. 9% of patients had high-risk phenotypes for *CYP2C19*, *CYP2D6*, and *ABCG2*, meaning prescribing recommendations apply for omeprazole/pantoprazole, voriconazole, ondansetron, tramadol, and allopurinol, all commonly prescribed supportive care medications for children with acute leukemia/lymphoma [40]. Without considering *ABCG2* (paired with allopurinol), 30% of patients had high-risk phenotypes for both *CYP2C19* and *CYP2D6*.

Confirmation of the potential utility of pharmacogenomics in pediatric oncology across a range of individual pharmacogenes, and in combination, supports a broader approach to PGx testing

TABLE 3 | Proportion of patients prescribed PGx medications and those classified as actionable.

Medication	Patients prescribed *n* (%)	Patients prescribed in conjunction with a high-risk variant (aPGx) *n* (% aPGx in patients taking the medication; *% of overall cohort*)
Ondansetron	158 (87.8%)	*CYP2D6*: 6 (3.8%; *3.3%*)
Omeprazole	69 (38.3%)	*CYP2C19*: 27 (39.1%; *15%*)
Mercaptopurine	42 (23.3%)	*TPMT*: 3 (7.1%; *1.7%*) *NUDT15*: 6 (14.3%; *3.3%*)
Pantoprazole	34 (18.9%)	*CYP2C19*: 8 (23.5%; *4.4%*)
Voriconazole	27 (15%)	*CYP2C19*: 12 (44.4%; *6.7%*)
Allopurinol	22 (12.2%)	*ABCG2*: 0 *HLA-B*: 0
Tramadol	15 (8.3%)	*CYP2D6*: 3 (20%; *1.7%*)
Amikacin	9 (5%)	*MT-RNR1*: 0
Sertraline	5 (2.8%)	*CYP2B6*: 0 *CYP2C19*: 2 (40%; *1.1%*)
Rasburicase	5 (2.8%)	*G6PD*: 0
Tacrolimus	4 (2.2%)	*CYP3A5*: 0
Amitriptyline	3 (1.7%)	*CYP2D6*: 0 *CYP2C19*: 0
Flucloxacillin	3 (1.7%)	*HLA-B*57:01*: 0
Oxcarbazepine	2 (1.1%)	*HLA-B*15:02*: 0
Tioguanine	2 (1.1%)	*TPMT*: 0 *NUDT15*: 0
Irinotecan	2 (1.1%)	*UGT1A1*: 0
Methylene blue	1 (0.6%)	*G6PD*: 0
Codeine	0 (0%)	—
Nortriptyline		
Flecainide		
Fluvoxamine		
Citalopram		
Paroxetine		
Tropisetron		
Fluorouracil		
Capecitabine		
Carbamazepine		
Simvastatin		

than a single pharmacogenetic test or even a panel. Importantly, panel PGx tests are commonly developed using alleles identified in homogeneous European populations and their use may result in misinformed guidance for populations with a more diverse ancestry [41]. The benefits of using a WGS approach to identify PGx variants in a diverse ancestry cohort have been demonstrated elsewhere [42]. However, the cost of WGS for this purpose remains prohibitive. In Australia, WGS is only Medicare funded for children under 11 years of age where a monogenic condition is suspected [43]. Even with this funding, out-of-pocket costs can be expected [43]. Without Medicare funding (including for PGx analysis) WGS costs approximately $4300 AUD per patient. Whilst it is expected WGS will become more affordable as usage increases, cost is still a barrier. By comparison, a CYP panel costs patients just under $200 AUD [44]. However, given the increasing availability of WGS data for oncology patients for diagnostic purposes and to guide cancer therapy choice, it is pragmatic to repurpose this data for additional clinical uses such as PGx analysis. This approach reduces costs and procedures associated with stand-alone PGx testing, allows for flexibility in gene selection, and is more accurate and equitable in a diverse population.

There are some limitations to the clinical application of the results of this study. Phenoconversion should be accounted for when predicting phenotypes, and is one of the cited barriers to adopting clinical PGx guidelines [29, 45]. While only five patients in this study were assessed as potentially CYP2D6 phenoconverting, there were a significant number that may be susceptible to CYP2C19 phenoconverting. Further studies are needed to better predict the effects of CYP2C19 inducers and inhibitors on metabolizer states as data has been conflicting thus far [30, 31]. Additionally, phenoconversion can occur due to factors such as inflammation, disease, and obesity, although assessment of these was outside the scope of this study [45]. Efforts should be made to design a medication response prediction model that factors in genetics, concomitant medications, disease, comorbidities, and inflammation.

The impact of ontogeny on result interpretation should also be considered; for example, children < 1 year old are known to have reduced *CYP2D6* activity, and existing PGx prescribing guidelines may not be appropriate [5]. Additionally, many medications such as ondansetron are metabolized via multiple pathways, yet recommendations are based only on one pathway. For more precise guidelines, additional metabolism pathways for medications should be assessed and incorporated into guidelines where possible. In this study, medication histories were captured at four specific timepoints over a 12-week period, likely underestimating the actionability estimates for each medication. Actionability may also be underestimated due to guidelines containing recommendations to avoid specific medications. Additionally, this study only examined a small cohort of Australian patients from one region in Australia and may not be representative of the entire Australian population. Results should be validated in a larger study, including patients from other centres in Australia. Finally, the ancestral groups recorded in this study were self-reported and may be imprecise. Whilst the challenges of self-reported ancestry have been previously described [46], genetically determining ancestry was outside the scope of this study.

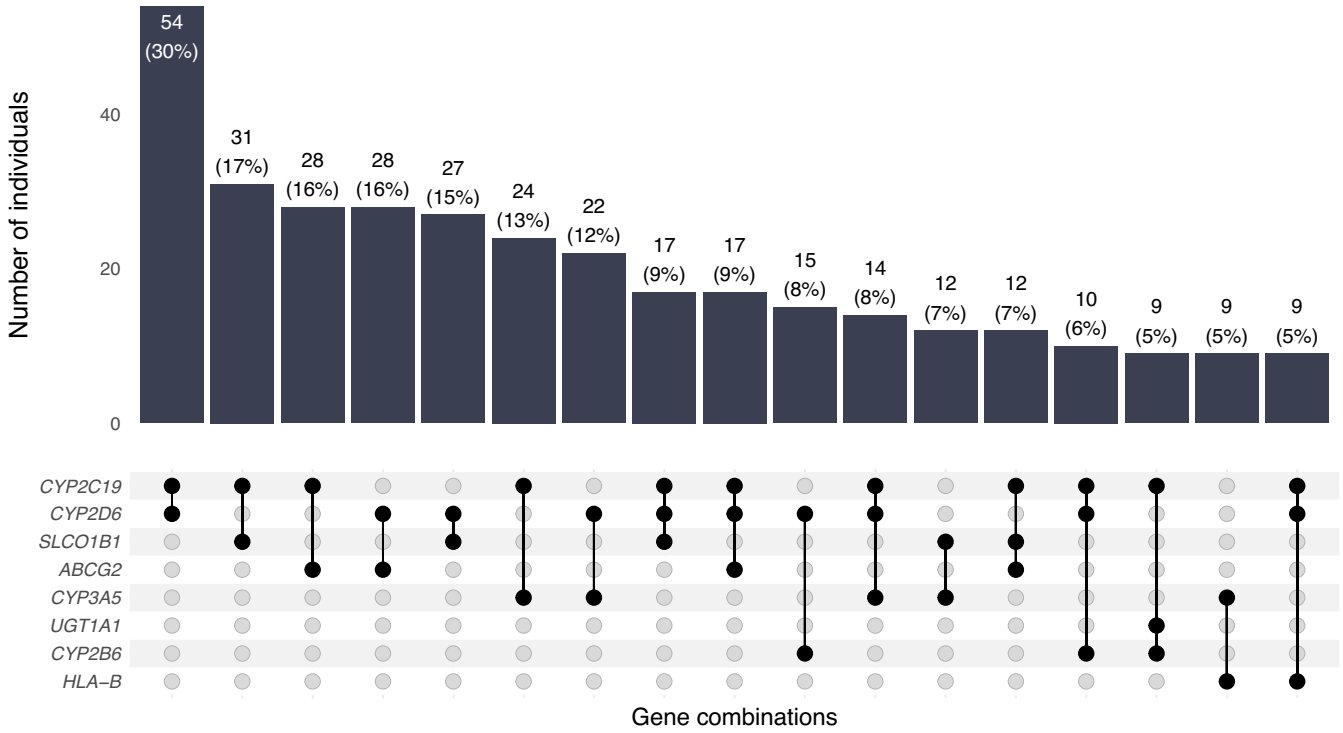

FIGURE 4 | Gene combinations identified with at least 5% frequency. Numbers in brackets denote the percentage of the total cohort.

Whilst the implementation of pre-emptive PGx in pediatric oncology has the potential to significantly impact clinical care, evidence confirming the utility is yet to be produced. The MARVEL-PIC trial was designed to provide this evidence and we await reporting of the primary outcome—a reduction in ADRs in patients with an actionable PGx variant after PGx test results are used to guide therapy [14]. Future PGx discovery studies should look to incorporate phenoconversion (such as the PEGASUS study) [47] as well as considering multiple routes of metabolism for medications. Additionally, efforts should be made to further investigate the role of CYP enzyme polymorphisms in the metabolism of chemotherapeutics such as cyclophosphamide and vincristine. These agents are both known to be metabolized at least in part by CYP enzymes, and there have been some reports of CYP genotype associated differences in drug response and survival [48, 49]. Future oncology prescribing should incorporate detailed knowledge of the pharmacokinetics and pharmacodynamics of all chemotherapy and supportive care medications to improve patient outcomes.

5 | Conclusion

We identified a high frequency of clinically relevant high-risk PGx phenotypes in a diverse Australian pediatric oncology cohort. This study paves the way for using the identified combinations of pharmacogenes in supportive care prescribing in oncology and is critical for the eventual implementation of pre-emptive pharmacogenomic testing in pediatrics. However, for more accurate PGx phenotype prediction, phenoconversion adjustments will need to be incorporated once clear consensus guidelines exist. Furthermore, our approach to repurposing WGS data for pre-emptive PGx testing is feasible, capitalizes on existing resources and is preferred as it enables flexibility for PGx discovery as well as being more equitable. As evidence for PGx prescribing mounts, and more pharmacogene-drug guidelines are developed, the utility of this approach will only increase.

Author Contributions

C.M., A.H., T.S., D.K., E.W., R.D., J.S., D.A.E., and R.C. wrote the manuscript; C.M., R.C., and A.H. designed the research; C.M., A.H., and R.C. performed the research; C.M., A.H., and R.C. analyzed the data.

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Conflicts of Interest

The authors declare no conflicts of interest.

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