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Kristie N. Ramos

David Gregornik

Kenneth S. Ramos

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Kristie N. Ramos[a], *David Gregornik*[b] *and Kenneth S. Ramos*[c]

Purpose of review
Pharmacogenomic insights provide an opportunity to optimize medication dosing regimens and patient outcomes. However, the potential for interindividual genomic variability to guide medication dosing and toxicity monitoring is not yet standard of care. In this review, we present advances for the thiopurines, anthracyclines and vincristine and provide perspectives on the actionability of pharmacogenomic guidance in the future.

Recent findings
The current guideline on thiopurines recommends that those with normal predicted thiopurine methyltransferase and NUDT15 expression receive standard-of-care dosing, while 'poor metabolizer' haplotypes receive a decreased 6-mercaptopurine starting dose to avoid bone marrow toxicity. Emerging evidence established significant polygenic contributions that predispose to anthracycline-induced cardiotoxicity and suggest this knowledge be used to identify those at higher risk of complications. In the case of vincristine, children who express CYP3A5 have a significantly reduced risk of peripheral neuropathy compared with those expressing an inactive form or the CYP3A4 isoform.

Summary
The need for adequately powered pediatric clinical trials, coupled with the study of epigenetic mechanisms and their influence on phenotypic variation and the integration of precision survivorship into precision approaches are featured as important areas for focused investments in the future.

Keywords
chemotherapeutic agents, pharmacogenomics, precision oncology

INTRODUCTION

Pharmacogenomics is one of the earliest and most impactful applications of genetic insight into the practice of medicine; with its roots tracing back to the recognition that genetic variation in the enzymes involved in drug metabolism can significantly impact drug response and toxicity [1]. With the advent of advanced high throughput molecular technologies, the field of pharmacogenomics continued to evolve from the study of single genes and enzymes to genome-wide assessments of individualized drug responses. Pharmacogenomic insights pose an opportunity for providers to optimize medication dosing regimens based on the genetic characteristics of individual patients, and while it has yet to become standard of care, preemptive pharmacogenomics testing has gained considerable popularity among patients and their families, as well as medical providers. The application of pharmacogenomics-based interventions in pediatric oncology is of particular interest, however significant challenges to widespread implementation remain.

To help facilitate the use of genotype results in medical decision-making, the Clinical Pharmacogenetics Implementation Consortium (CPIC) was established to provide freely accessible peer-reviewed, and evidence based guidelines for gene-drug pairs that can be utilized to incorporate pharmacogenomic results into patient care. To date, CPIC has created and curated information on

[a]St. Louis Children's Hospital, Washington University School of Medicine, St. Louis, Missouri, [b]Children's Minnesota Hospital, University of Minnesota, Minneapolis, Minnesota and [c]Institute of Biosciences and Technology, Texas A&M Health, Houston, Texas, USA

Correspondence to Kenneth S. Ramos, MD, PhD, Institute of Biosciences and Technology, Texas A&M Health, Houston, Texas, USA.
Tel: +1 713 677 7740; e-mail: kramos@tamu.edu

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KEY POINTS

- Although the lack of adequately powered clinical pediatric trials during development and post marketing surveillance of drugs continue to be major limitations, other barriers include the storage of genomic data in the electronic health record and the lack of coverage of genotype testing by many insurance plans.
- TMPT and NUDT15 metabolic phenotypes were among the first to be utilized in pharmacogenomic-mediated dose adjustments and continue to be of clinical significance in mitigating thiopurine toxicity.
- Numerous SNPs and genes have been associated with the development of Anthracycline-induced cardiotoxicity, with many of these genes involving the phosphatidylinositol signaling system, glycosylphosphatidylinositol-anchored proteins, axonal pathways, ATP-binding cassette transporters, and retinoic acid receptor.
- The role of the CYP3A subfamily of the cytochrome P450 monooxygenases in vincristine-induced peripheral neuropathy has been studied by several groups and highlights the potential role of pharmacogenes in interindividual differences related to drug bioavailability, efficacy, clearance, and toxicity.
- Complex gene-environment-lifestyle interactions likely account for many of the observed inconsistencies described in the medical literature for pharmacogenes, and clinicians must be cognizant that these genes, like other genes, are subject to complex interactions that define specific response profiles.

specific pharmacogenes with the goal of defining genetic variants associated with star allele haplotypes, assessing functional status for each haplotype, and assigning a predicted phenotype for each possible diplotype [2]. Although CPIC has certainly facilitated the translation of pharmacogenomic knowledge from the bench to the bedside, the potential for interindividual genomic variability to guide medication dosing and toxicity monitoring on a widespread level has yet to be fully actualized.

In this review, we focus on pharmacogenomic advances for three frequently used drug classes in pediatric oncology, with thiopurines being the only one for which specific CPIC recommendations are available in the United States, and with anthracyclines and vincristine chosen as representative classes of chemotherapeutic agents for which emerging pharmacogenomic evidence will likely inform clinical management in the future. Lastly, we provide perspectives on future advances in the field of precision pediatric oncology and the actionability of pharmacogenomic guidance in the future.

THIOPURINES

The thiopurines, including azathioprine, 6-mercaptopurine (6-MP), and thioguanine, were among the first identified drugs to be impacted by clinically significant genetic variations in drug-metabolizing enzymes. Both thioguanine and 6-MP are utilized in the treatment of pediatric acute lymphoblastic leukemia (ALL) and acute myeloid leukemia, and depending on the protocol, can be required for up to 2 years as an integral part of maintenance chemotherapy for pediatric ALL treatment [3]. Thiopurine toxicity is widespread and includes pancreatitis, hepatitis, sinusoidal obstruction syndrome, and myelosuppression [4▪], with variations in key enzymes (namely, TMPT and NUDT15) resulting in heightened risk for life-threating bone marrow toxicity [5].

The first thiopurine pharmacogene to be implicated in the development of thiopurine toxicity was TMPT, which catalyzes the methylation of 6-MP and its downstream metabolites to facilitate their removal and preclude any further bio-activation [6]. There is inherited variation in thiopurine methyltransferase (TPMT), with certain allelic variants resulting in increased production of thioguanine nucleotide metabolites and ultimately resulting in further nucleic acid damage and cell death [4▪]. To date, CPIC provides information on more than 40 star allele haplotypes for the TMPT enzyme [2], with different star alleles and suballeles having variable metabolic activity and predisposition to thioguanine toxicity [7]. This information has been used to assign pediatric patients with a metabolic phenotype (based on the predicted functional activity of their haplotype), and is subsequently used to designate normal, intermediate, or poor metabolizers of thiopurines.

To date, the ∗1 allele correlates with normal thiopurine metabolic function, TMPT2, ∗3A, ∗3B, ∗3C, ∗4, ∗11, ∗14, ∗15, ∗23, ∗30, and ∗41 are termed as 'no function' alleles, and all other star alleles are denoted to be of uncertain function. The most common TPMT phenotype is TPMT∗1/∗1, which accounts for 90% of enzyme variants across most bio-geographical and ancestral groups [8] and represents individuals that are 'normal metabolizers' of thiopurines. Alternatively, those that carry a star allele of uncertain function have been designated as 'possible intermediate metabolizers', those that carry a normal function allele in combination with a *no function* allele (e.g., TMPT ∗1/∗2 and TMP ∗1/∗3A) have been deemed as 'intermediate metabolizers', and those with two 'no function' alleles are considered to be 'poor metabolizers' of thiopurines. These metabolic phenotypes were among the first to be

utilized in pharmacogenomic-mediated dose adjustments and continue to be of clinical significance in mitigating thiopurine toxicity.

The second thiopurine pharmacogene of significance is NUDT15, which encodes for the nucleotide diphosphatase enzyme that catalyzes the conversion of active thiopurine metabolites into their inactive forms (thus preventing their incorporation into RNA and DNA) [9,10]. Although studies on the genetic variation of NUDT15 are relatively immature in comparison with those on TPMT, CPIC and the Pharmacogene Consortium have reported 20 star allele haplotypes in the *NUDT15* gene [2,10]. To date, NUDT15∗1 is considered to have normal function, NUDT15∗2, ∗3, and ∗9 are designated as 'no function' alleles, ∗4 through ∗8 are deemed as 'uncertain function', and ∗10 through ∗20 have yet to be annotated [2]. Accordingly, NUDT15∗1/∗1 is designated as a 'normal metabolizer', those with a normal function allele combined with a 'no function' allele are termed 'intermediate metabolizers', and those with two 'no function' alleles are predicted to be 'poor metabolizers' of thiopurines [2].

The CPIC guideline on thiopurines utilizes these pharmacogenomics insights to provide recommendations for initial dose selections as a function of both TMPT and NUDT15 genotypes [3] and serves as the most widely recognized example of the utility of pharmacogenomics in cancer therapeutics. Currently, those with normal predicted TPMT and NUDT15 phenotypes receive standard-of-care dosing for thiopurines (e.g., 6-MP at a starting dose of 75 mg/m^2/day during maintenance chemotherapy for pediatric ALL) [2], whereas those with 'poor metabolizer' haplotypes require a decreased 6-MP starting dose to avoid potentially life-threatening bone marrow toxicity, thus exemplifying one of the many ways in which the incorporation of pharmacogenomic knowledge can be utilized to decrease the risk of chemotherapy-related toxicities in pediatric oncology patients.

ANTHRACYCLINES

The anthracyclines, including doxorubicin and daunorubicin, are another important class of chemotherapeutic agents utilized in the treatment of a various pediatric leukemias, lymphomas, and sarcomas [11,12]. Anthracyclines function as antineoplastic drugs by intercalating into DNA, disrupting topoisomerase IIα-mediated DNA repair, and ultimately causing DNA damage and cellular apoptosis [13]. Despite the indication for anthracyclines in numerous chemotherapy protocols, their use is often complicated and subsequently limited by anthracycline-induced cardiotoxicity (ACT). ACT is widespread and ranges from asymptomatic systolic dysfunction to overt congestive heart failure [14,15], and while the exact mechanism of ACT continues to be debated, free-radical-mediated oxidative damage and mitochondrial dysfunction are believed to play a significant role in the development of cardiotoxicity [11,15].

ACT is dose-dependent and cumulative, with those receiving higher doses and chest irradiation at greater risk. Cardiotoxicity can be observed in patients treated with lower doses of doxorubicin or daunorubicin, indicating that variations in individual susceptibility can play a significant role in risk stratification [14,16,17]. Given that conventional biomarkers often remain within normal limits until myocardial damage has ensued, the detection of early and asymptomatic cardiotoxicity remains a critical challenge. With nearly 60% of all pediatric cancer survivors having a history of prior anthracycline and/or chest radiation exposure [18,19], there is an ongoing need to identify genetic risks, discover predictive biomarkers, and implement standardized screening protocols to mitigate life-threatening ACT.

To date, numerous single-nucleotide polymorphisms (SNPs) and genes have been associated with the development of ACT. In a genome-wide model that utilized International HapMap cell lines, 137 SNPs spanning 30 genes were found to be significantly associated with daunorubicin cardiotoxicity, with many of these genes involving the phosphatidylinositol signaling system, glycosylphosphatidylinositol-anchored proteins, and axonal pathways [20]. Subsequent studies found that polymorphisms in genes encoding for ATP-binding cassette (ABC) transporters were associated with ACT [21–24], with ABCB1 rs2235047 and ABCC1 rs4148808 variants associated with a higher risk of ACT across various pediatric malignancies [23,24], and the ABCC5 rs7627754 TT genotype [21] as well as ABCC1 gene variants (rs3743527 and rs246221) associated with ACT in pediatric ALL [22]. On a larger scale, the rs6759892 variant in UGT1A6 (which encodes for a glucuronosyltransferase) has been found to be significantly associated with the development of ACT [23–25], and more recently, a genome-wide association study implicated the missense variant rs2229774 in Retinoic acid receptor gamma (RARG) (which encodes for a retinoic acid receptor) with heightened susceptibility to ACT [26]. Conversely, variants in genes encoding for solute carriers (which play an important role in the absorption and excretion of drugs) appear to confer a lesser risk of ACT, with the genetic variants rs7853758 in SLC28A3, rs9614091 in SLC10A2, and rs4877847 in SLC28A3 found to be protective against the development of ACT for more than 5 years after completion of

anthracycline therapy [23,24]. Together, these data highlight the polygenic contributions that predispose to the development of ACT and suggest that it may be possible to discriminate between those at higher and lower risk for development of this life-threatening complication.

These pharmacogenomics data have been utilized to develop evidence-based clinical practice recommendations by the Canadian Pharmacogenomics Network for Drug Safety, whose Clinical Practice Recommendations Group suggests pharmacogenomic testing for UGT1A6∗4 rs17863783, RARG rs2229774, and SLC28A3 rs7853758 variants in pediatric cancer patients with an indication for doxorubicin or daunorubicin therapy [27]. Future directions include the incorporation of additional genetic, epigenetic, and clinical risk factors to guide anthracycline dosing and frequency of biomarker monitoring with the goal of eventually implementing practice guidelines to mitigate the risk of ACT.

VINCRISTINE

Vincristine is another frequently used chemotherapeutic agent in the treatment of several pediatric malignancies, and functions as an antineoplastic drug by interfering with microtubule formation during mitotic spindle assembly, which ultimately leads to cell death [28]. Vincristine therapy is commonly associated with a severe, dose-limiting peripheral sensory-motor neuropathy [29–31] that typically resolves within a few months of cessation of therapy, however severe neurotoxicity is not experienced by all patients [32]. The pattern of selective vincristine-induced peripheral neuropathy (VIPN) suggests that an individual's response to vincristine is subject to genetic, environmental, and/or lifestyle factors. To date, most pharmacogenomics studies of VIPN-affected children have emphasized DNA sequence variations with lesser attention given to the influence on epigenetic modifiers on genome function.

The role of the CYP3A subfamily of the cytochrome P450 monooxygenases in VIPN has been studied by several groups and highlights the potential role of pharmacogenes in interindividual differences related to drug bioavailability, efficacy, clearance, and toxicity. The CYP3A subfamily includes CYP3A4, CYP3A5, CYP3A7, and CYP3A43, along with four pseudogenes and several functionally relevant transcript variants [33,34]. Children who express the CYP3A5 isoform have been found to have a significantly reduced risk of VIPN in comparison with those who express either an inactive form of CYP3A5 or an active form of CYP3A4 [35–37]. Several allelic variants of CYP3A5 have been identified, with the CYP3A5 ∗1/∗1 expressers on one end of the genotypic spectrum and CYP3A5 nonexpressers (∗3/∗3 genotype) on the other, with those expressing at least one copy of the CYP3A5 ∗1 allele found to exhibit greater expression than those who are homozygous for other variants. CYP3A5 ∗3 creates a premature codon that alters mRNA splicing and results in a truncated protein [38], and as a result, CYP3A5 ∗3 homozygous individuals produce attenuated levels of functional CYP3A5 protein. Given that vincristine is preferentially metabolized by CYP3A5 [39,40], its clearance is dependent on the presence of a functional CYP3A enzyme. As a whole, Asians and African Americans have a higher prevalence of nonfunctional CYP3A5 alleles (CYP3A5 ∗6, ∗7), while a relatively large percentage of Caucasians express a CYP3A4 ∗22 isoform with intermediate metabolic capacity [41▪], suggestive of an increased risk for VIPN in these subpopulations and the potential use of CYP3A4 and CYP3A5 activity as future biomarkers for vincristine efficacy and toxicity.

Beyond the impact of the CYP3A subfamily on vincristine metabolism, Ceppi *et al.* [42] reported inverse associations between VIPN and variants of ABCB1 and capping actin protein, gelsolin like (a member of the gelsolin/villin family of actin-regulatory proteins). Variable associations have also been reported for ABCC1 [43] and SLC5A7 (Solute Carrier Family 5 Member 7) [44], with SLC5A7 of potential interest from a pathogenetic perspective given its role in autosomal dominant distal hereditary motor neuronopathy type VIIA and the presence of multiple splice variants that contribute to inter-individual variability [45]. Lastly, a genome-wide association study of pediatric ALL patients conducted by Diouf *et al.* [46] reported that the severity of VIPN was higher in children with a SNP in the promoter region of CEP72 (a centrosomal protein involved in microtubule assembly), though no such association was identified by Gutierrez-Camino *et al.* [47] in a Spanish pediatric ALL cohort. Additional studies are required to reconcile these inconsistencies and examine the contributions of additional genes involved in drug transport, microtubule assembly, and neuronal function to further elucidate the genetic and epigenetic causes of vincristine-induced peripheral neuropathy.

CONCLUSION

Pharmacogenes can account for major interindividual differences in drug bioavailability, efficacy, clearance, and toxicity. Genetic polymorphisms are able to partially explain this variability, and when the data are available, allow stratification of individual patients into metabolic phenotype

categories, although these genotype–phenotype relationships are infrequently considered due to a general lack of evidence-based recommendations to guide clinical decision making. In this mini-review, we highlighted three drug classes with noteworthy pharmacogenomic insights, with thiopurines as the only class to have widely recognized and accepted pharmacogenomics-based dosing guidelines. Although perhaps the most significant limitation to the implementation of pharmacogenomics is the lack of adequately powered pediatric clinical trials during development and postmarketing surveillance of drugs, other barriers include the storage of genomic data in the electronic health record and the lack of coverage of genotype testing by many insurance plans.

Additional research is needed to evaluate phenotypic variations in pharmacogenes that are mediated via epigenetic mechanisms. This is an important dimension of genomics research that remains largely underdeveloped in the field of pharmacogenomics, a somewhat surprising finding when considering the potential impacts of xenobiotics, diet, and lifestyle choices (such as smoking and alcohol use) on drug metabolizing enzymes. It is likely that complex gene-environment–lifestyle interactions account for many of the observed inconsistencies described in the medical literature, and clinicians must be cognizant that pharmacogenes, like other genes, are subject to complex interactions that define specific response profiles. As such, development of precision-based approaches to account for such interactions is necessary to personalize drug treatments in ways that optimize clinical efficacy and minimize toxicity.

Finally, it is important to integrate the principles of precision survivorship into the practice of precision medicine. Clearly, the chemotherapeutic and cell-based therapies being utilized in pediatric populations have long-lasting consequences on the health and wellbeing of these patients. In an era where childhood cancer survivors are living years beyond their diagnosis, efforts should be made to capitalize on the advances in genomic medicine to mitigate the side effects of chemotherapy and preserve the quality-of-life of patient survivors for the years to come.

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Conflicts of interest

There are no conflicts of interest.

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