Using Germline Genomics to Individualize Pediatric Cancer Treatments

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Abstract
The amazing successes in cure rates for children with cancer over the last century have come in large part from identifying clinical, genetic, and molecular variables associated with response to therapy in large cooperative clinical trials and stratifying therapies according to the predicted risk of relapse. There is an expanding interest in identifying germline genomic variants, as opposed to genetic variants within the tumor, that are associated with susceptibility to toxicity and for risk of relapse. This review highlights the most important germline pharmacogenetic and pharmacogenomic studies in pediatric oncology. Incorporating germline genomics into risk-adapted therapies will likely lead to safer and more effective treatments for children with cancer.

Introduction
The majority of children with cancer receive treatment that is tailored according to their predicted risk of relapse, based on a combination of clinical features, peripheral blood markers, and tumor genetics (1–4). This approach has led to significant improvement in the outcome of patients with a broad range of pediatric cancers. However, within risk groups, it remains difficult to predict which children are at greatest risk of experiencing chemotherapy-related toxicities and/or nonresponse. Pharmacogenomics is the study of the genetic basis for individual differences in drug efficacy and/or toxicity, with the goal of identifying patients at risk for severe toxicity and/or nonresponse before initiation of therapy. Although most pediatric oncology centers do not routinely use pharmacogenetic or genomic testing, recent studies have shown that germline genetic biomarkers can be used to personalize therapy and improve the overall care of children with cancer. In this review, we provide an overview of clinical and preclinical studies aimed at identifying genomic markers for risk of toxicity or nonresponse in pediatric cancers, describe the results of genome-wide studies, and discuss how these findings can be translated into improved care for pediatric cancer patients.

The U.S. Department of Health and Human Services has developed strength-of-evidence guidelines for the implementation of pharmacogenetic testing and subsequent therapy modifications (PharmGKB, http://www.pharmgkb.org/download.action?filename=PGKB-levels_of_evidence.pdf). The highest level of evidence (level 1) requires replication in populations of at least 1000 cases and 1000 controls of the same ethnicity, and P-values < 0.05 after multiple testing correction. Given the relative rarity of childhood malignancies and the paucity of identified actionable pharmacogenetic variants in pediatric oncology patients, it will be difficult to obtain level 1 evidence to support the implementation of pharmacogenomic testing into clinical practice in this patient population. However, we are in a time of rapidly increasing knowledge about the human genome, and the selected studies relevant to pediatric oncology highlighted in this review (summarized in Table 1) illustrate the exciting potential of this field for moving us closer to individualized therapy based on risk of toxicity and nonresponse to chemotherapeutic agents (refer to Fig. 1 for a hypothetical example of pharmacogenetics in action).

Germline Genome Variation and Chemotherapeutic Toxicity
The majority of germline pharmacogenetic or pharmacogenomic studies in pediatric oncology have focused on identifying variants associated with toxicity. Although variability in tumor response is thought to lie within the realm of acquired somatic mutations within the tumor, recent studies have shown that germline variants also contribute to response (5–9). Investigators have identified variants within known metabolic or pharmacokinetic pathway genes that have a large effect on chemotherapeutic drug metabolism using a candidate gene approach. It stands to reason that variants that would affect the ability of drug-metabolizing enzymes (DME) to degrade active metabolites would lead to untoward effects. More recently, whole-genome studies have unveiled genetic variants in noncoding regions or within genes not previously implicated in the...
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pharmacokinetic or pharmacodynamic pathways of a given drug, broadening our understanding of how genetic variation influences drug toxicity and efficacy (Fig. 2; refs. 8–11).

The best-studied example of genetic variation within a DME and its effect on toxicity is the interaction between variants in thiopurine methyltransferase (TPMT) and toxicity with the thiopurine antimetabolites 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG). 6-MP is used as an immunosuppressant for some nonmalignant conditions, such as inflammatory bowel diseases (12, 13), and is one of the backbone treatments in the most frequent pediatric malignancy, acute lymphoblastic leukemia [ALL (14)]. The thiopurines are prodrugs that are converted by multiple enzymes into thioguanine nucleotides (TGN), which are then incorporated into DNA. Inactivation of TGN occurs by 2 main mechanisms: oxidation by xanthine oxidase and methylation by TPMT. Xanthine oxidase activity is negligible in hematopoietic tissues, so these cells rely on TPMT for TGN inactivation (15).

Struck by the wide interpatient variability in both response and toxicity observed in patients treated with 6-MP, Weinsilboum and Sladek (16) first described patients with absent erythrocyte TPMT activity. Based on the distribution of enzyme activity in the general population, they hypothesized that TPMT enzyme activity is inherited in a codominant fashion, and that patients with 2 nonfunctional alleles will experience severe, life-threatening myelosuppression with continuous conventional dosing of 6-MP, and 30% to 60% of heterozygotes cannot tolerate full doses of 6-MP (23, 24). Pharmacogenetic dosing of 6-MP was done on the St. Jude ALL Protocol Total XIIIB (25). Homozygous WT patients (n = 231) were given a standard postremission maintenance dose of 75 mg/m² daily and heterozygous variant patients (n = 15) were given 60 mg/m². With this dosing strategy, there were no observed differences in the cumulative incidence of relapse between the 2 dosing groups (P = 0.43). A follow-up analysis showed that 25% of heterozygous variant patients were taking a 6-MP dose reduced by ≥30% at the end of therapy, compared with only 3% of WT patients (26). There was no difference in the cumulative incidence of toxicities between the 2 dosing groups (26). Although these results represent a very small cohort of heterozygous patients and no homozygous variant patients, there seems to be no impact of dose reduction on efficacy or toxicity in patients with a reduced ability to inactivate 6-MP. Based on the experiences with inflammatory bowel disease, thiopurine dose modifications based on TPMT activity to prevent severe neutropenia are now recommended in a black box warning by the U.S. Food and Drug Administration, and have been adopted widely in the treatment of autoimmune disease and at St. Jude and other centers in the treatment of

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<td>Yang et al. (2010)</td>
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childhood ALL (21, 27). Although commercially available genetic testing options change over time, Prometheus Laboratories (San Diego, CA) and Specialty Laboratories (Valencia, CA) offer Clinical Laboratory Improvement Amendments (CLIA) certified testing for \( TPMT^{2}, TPMT^{3A}, TPMT^{3B}, \) and \( TPMT^{3C}, \) and some insurance companies cover preemptive \( TPMT \) genetic testing. Given the strength of evidence for the relationship between \( TPMT \) genotype and tolerance of thiopurines, we believe a large collaborative trial evaluating the safety, efficacy, and cost-effectiveness of pharmacogenetic dosing of 6-MP based on \( TPMT \) genotype in patients with ALL, in similarity to the St. Jude approach, is warranted.

Another widely recognized gene–drug interaction in pediatric (and adult) oncology is the relationship between irinotecan (a camptothecin analog and topoisomerase 1 inhibitor) and one of its metabolizing enzymes, UGT1A1. Irinotecan, which is used in the treatment of rhabdomyosarcoma as well as refractory solid tumors, is converted by carboxylesterases to the active antitumor agent SN-38. SN-38 is glucuronidated to allow for excretion by UGT1A1. A 7-TA repeat variant within the promoter of \( UGT1A1 \), referred to as \( UGT1A1^{28} \) (rs8175347), leads to decreased enzyme activity (29). Patients homozygous for this variant have impaired inactivation of SN-38 and are at high risk for severe irinotecan toxicity, including neutropenia and diarrhea (30). These genotype-toxicity relationships appear to be particularly significant at higher doses.

Figure 1. The promise of pharmacogenetics. By making associations between genotype and characteristic phenotypes (e.g., toxicity and nonresponse), physicians can use pharmacogenetics to choose medication doses that are appropriate for a patient’s expected response. This approach has the potential to minimize toxicity and maximize efficacy by reducing dose interruptions and severe toxicities.
Dose-finding strategies based on UGT1A1 genotype have been attempted in adult clinical trials, but have yet to be incorporated into pediatric trials, despite the increased use of irinotecan in both upfront and relapse clinical trials (32, 33). Of interest, in a Spanish study of 94 patients with advanced colorectal cancer who were being treated with 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI), a dose-finding study of irinotecan by UGT1A1 genotype revealed that homozygous WT (C3/C3) and heterozygous (C3/C3.28) patients could tolerate significantly higher doses of irinotecan (450 mg/m² and >250 mg/m² administered every 21 days (31)).
390 mg/m², respectively) than the recommended dose of 180 mg/m² (33). Pharmacogenetic testing for UGT1A1 has not been incorporated into upfront pediatric trials, but these results suggest that dose-finding studies should be undertaken in pediatrics by UGT1A1 genotype to optimize dose intensity while maintaining low toxicity. Similarly to the case of 6-MP, there is a black box warning on the label related to UGT1A1, but because the diarrhea and neutropenia induced by irinotecan toxicity can be managed medically, only a handful of centers have adopted routine pharmacogenetic testing.

Investigators have made important findings by broadening the study of single metabolic genes to the simultaneous evaluation of hundreds of known metabolizing genes on a commercial or custom-made chip. Several such chips are on the market, including the DMET chip (Affymetrix), which contains 1,936 single nucleotide polymorphisms (SNP) in 230 drug-metabolism genes; the VeraCode ADME chip (Illumina), which interrogates 184 SNPs in 34 drug-metabolism genes; and the iPLEX ADME pharmacogenomic panel (Sequenom, Inc.), which evaluates 192 polymorphisms across 36 pharmacogenetically relevant genes. In addition to commercial pharmacogenomics panels, some research groups have used custom-made chips that contain an array of variants within DMEs.

Platinum compounds comprise one of the most widely used and successful groups of cytotoxic drugs worldwide and are used in the first-line treatment of testicular cancer, neuroblastoma, osteogenic sarcoma, and brain tumors. Until recently, there were no means of identifying patients at risk for developing significant platinum toxicities, including ototoxicity (34). Ototoxicity occurs in up to 60% of patients receiving cisplatin, and in children this toxicity can be particularly debilitating because it can affect cognitive and emotional development by impairing receptive language (35–37). Using a custom-made ADME chip with 1,949 genetic variants in 220 drug-metabolizing genes, Ross and colleagues (38) evaluated the risk of developing ototoxicity in children treated with cisplatin. In a test cohort of 54 children and validation cohort of 112 children, they identified variants in both TPMT and COMT (enzymes that were not previously identified as being involved in cisplatin metabolism) that were strongly associated with the development of cisplatin-induced ototoxicity. In fact, unique carriers of either risk allele were 12.1 times more likely to experience ototoxicity than noncarriers (\(P = 3.4 \times 10^{-5}\)), and variants in one or both of these genes were able to explain nearly half of all ototoxicity cases in the series (38). These findings are significant; however, less ototoxic platinating agents, such as carboplatin (39), have not always shown equal efficacy to cisplatin (40), suggesting that a drug switch may adversely affect outcomes. An alternative approach would be to prospectively randomize children to receive emerging otoprotective strategies (41–43) with cisplatin-based chemotherapies, and assess their impact by TPMT and COMT genotype.

Anthracyclines are commonly used to treat leukemias, lymphomas, and solid tumors, but can cause anthracycline-induced cardiotoxicity (ACT) in up to 57% of children (44, 45). In a similar analysis with 440 patients (156 test patients and 284 validation patients), Visscher and colleagues (46) used a custom-made genotyping chip of 2,977 SNPs in 220 drug-metabolism genes. They found that a variant within the solute transport carrier SLC28A3 was protective against the development of ACT, and several variants were moderately associated with either the development of or protection from ACT. Using combinations of the nine most significant variants (located in various transporters and DMEs), they were able to accurately predict which patients were at low, intermediate, or high risk of developing ACT following treatment with anthracyclines (46). These studies highlight discoveries that have the potential to substantially affect future treatment of pediatric malignancies. For example, if a patient has germline variants that are predictive for a high risk of developing of ACT, the cardioprotective agent dexrazoxane could be administered to mitigate this risk (47).

Broader genomic studies [referred to as genome-wide association studies (GWAS)] that look across the entire genome for variants associated with chemotherapeutic toxicities without bias to DMEs have yielded important novel findings as well. Results from these studies will allow for the creation of multigenic models to more accurately predict a given patient’s risk of toxicity. Asparaginase is used to treat ALL in children, but is associated with hypersensitivity in up to 45% of patients (48). A GWAS interrogating >500,000 SNPs across the genome in 485 children (322 patients in the discovery cohort, and 163 in the validation) with ALL for asparaginase hypersensitivity identified an overrepresentation of an SNP in an intron of the gene GRIA1, an SNP that had been implicated in bipolar disorder and schizophrenia but was not previously recognized as having an impact on immune function (10). This discovery would never have come about in a focused candidate gene or DME screen, and highlights the ability of GWAS to provide new biologic insights into common medical problems such as adverse drug reactions.

**Germline Genomic Variation and Chemotherapeutic Response**

Studies to determine the role of germline genetic variation in tumor response to cancer chemotherapies have begun to emerge. Risk stratification and, in some cases, targeted therapies based on unique genetic or genomic alterations within tumors (i.e., the BCR-ABL fusion oncoprotein in acute lymphoblastic and chronic myelogenous leukemia) have led to improvements in cure rates and likely reinforced the general belief that germline genomic variation plays a very small role in tumor response to chemotherapy. However, a small but ever-expanding body of literature shows that common germline variation is important for identifying not only patients at risk for toxicity but also patients at risk for nonresponse (5–9).

Genetic variants within glutathione-S-transferases, phase II DMEs that are important in the metabolism of several cancer
chemotherapies (e.g., anthracyclines, vincristine, etoposide, and corticosteroids) have been associated with response (5). In a matched case control study of 68 children with intermediate- and high-risk ALL (34 cases and 34 controls), Stanulla and colleagues (6) examined missense mutations within the GSTP1 enzyme and found that homozygotes for rs1695 (isoleucine to valine substitution at position 105 in GSTP1) had a significant reduction in risk of central nervous system (CNS) relapse [HR 0.09; 95% confidence interval (CI), 0.01–0.91; \( P = 0.04 \)]. The authors suggested that impaired detoxification ability in homozygous patients led to increased active drug exposure and reduced the risk of CNS relapse. Similar findings were reported in a retrospective analysis of 97 patients with Hodgkin lymphoma, in which the valine substitution in GSTP1 was found to be associated with survival after treatment in a dose-dependent manner. At 5 years, patients homozygous for the valine substitution (11%) had an overall survival (OS) of 100%, heterozygotes (37%) had an OS of 74%, and isoleucine homozygotes (52%) had an OS of 45%. In a Cox multivariate analysis, the presence of the valine allele was an independent prognostic feature for survival [HR 0.4; 95% CI, 0.21–0.85; \( P = 0.02 \) (7)]. These findings were generated from small retrospective analyses and have yet to be validated in prospective clinical trials; however, they offer important insight into the biology of treatment failure, and highlight patients who may be ideal candidates for therapy intensification (i.e., GSTP1 Ile/Ile patients).

Yang and colleagues (8) interrogated the germline SNP genotypes of 318 pediatric patients with ALL who had been treated at St. Jude Children’s Research Hospital and a validation cohort of 169 children who had been treated in Pediatric Oncology Group study 9906. They identified 102 SNPs that were significantly associated (\( P < 0.0125 \)) with the presence of minimal residual disease at the end of induction chemotherapy, and 21 of these were associated with disease relapse (8). Several of the top SNPs were within the IL15 gene, a proliferation-enhancing cytokine that was previously linked to glucocorticoid resistance, and were associated with a more aggressive ALL clinical presentation and an increase in CNS relapse (49–51). Several of the SNPs in IL15 that were implicated in this GWAS were also previously associated with increased transcription or translation efficiency in vitro (52), lending functional significance to these variants. Additionally, of the top 102 SNPs associated with the presence of minimal residual disease, 62% were also associated with one or more relevant phenotypes, such as rapid response to therapy or antileukemic drug pharmacokinetics (8).

In other studies, built on clinical observations of ethnic disparities in survival, patients of African American or Hispanic descent had worse outcomes than Asian or Caucasian patients (53–55). To investigate the influence of genetics on these observed disparities, Yang and colleagues (9) interrogated the germline SNP genotypes of 2,534 children with ALL alongside reference Caucasian, West African, East Asian, and Native American populations. They found that the component of genomic variation that cosegregated with Native American ancestry was associated with a risk of relapse (\( P = 0.0029 \)), even after adjusting for known prognostic features such as age, white count at diagnosis, and chromosomal aberrations (\( P = 0.017 \)), making this feature an independent prognostic factor (9). Of interest, these differences in outcome were abrogated in a subset of patients who received more intensive therapy (9), suggesting that variants that are important in drug resistance may cosegregate with Native American ancestry, and that this resistance can be overcome by additional therapy. The highest-ranked SNP associated with hematologic relapse was rs6683977 within the gene PDEAB (\( P = 2.2 \times 10^{-8} \)), and admixture mapping showed that local Native American ancestry in this genomic area was also strongly associated with hematologic relapse [\( P = 3.2 \times 10^{-9} \) (9)]. These findings highlight that some genetic variants associated with the phenotype of interest may be unique to a certain population, or may have higher allelic frequencies in a certain population to account for ethnic differences in the phenotype. Taken together, these GWASs represent important first steps in understanding the biology of treatment failure, and lay critical groundwork for future GWASs in pediatric oncology.

Cell-Based Models to Identify Genetic Markers

For children with cancer, it is difficult to employ a GWAS to identify heritable genetic variants associated with the response and/or toxicity of single drugs, because virtually all such patients are treated with multi-agent chemotherapy regimens. Furthermore, large cohorts are required for pharmacogenomic discovery, and replication sets are not readily available. Therefore, Dolan and colleagues (56, 57) developed cell-based models that can be used for discovery, confirmation, and/or functional studies of significant variants. The cell-based GWAS results can serve as a discovery mechanism for variants associated with in vitro resistance and help annotate clinical GWAS of response or toxicity. Susceptibility to chemotherapeutic-induced cytotoxicity was assessed in >500 well genotyped human Epstein–Barr virus (EBV)-immortalized lymphoblastoid cell lines derived from healthy individuals in the International HapMap Project (58–60). Because the HapMap Project includes cell lines derived from individuals representing 11 distinct ethnic groups (with ~90 individuals per ethnic group), it can also be used as a tool to discover the genetic contribution to pharmacoeconomic differences in chemotherapeutic susceptibility (61–63). Although EBV transformation may introduce a potential confounder of cellular sensitivity to a drug (64), the Dolan laboratory has not found any association between EBV copy number and pharmacological phenotypes (65). Each cell line’s unique sensitivity to drug-induced cell growth inhibition is measured, and the phenotypes are then subjected to GWAS using the publicly available HapMap genotypes to associate chemotherapy-related sensitivity with germline SNPs. This cell-based method is unique in...
that it represents an unbiased, comprehensive (genome-wide) approach that takes into consideration the multigenic nature of cellular susceptibility to a drug (Fig. 3). More recent studies have shown the potential of this cell-based approach for identifying clinical germline predictors of treatment outcome and functionally validating SNPs or genes identified in a clinical GWAS (66–69).

To investigate whether this model can also be used to identify genetic markers predictive of outcome in children with pediatric cancer, we are currently testing the association of platinating agent-resistant SNPs identified in the preclinical model and outcome in a cohort of >3,000 patients with neuroblastoma for whom whole-genome data are available. We have identified a significant enrichment of cell-based SNPs associated with resistance to cisplatin in patients with poorer event-free survival (N. Pinto and colleagues, unpublished data). There are ongoing studies to identify the function of these variants. Thus, clinically validated germline genetic biomarkers may provide new tools that can be used to individualize treatment for children with neuroblastoma and other pediatric cancers.

Conclusions and Future Directions

The studies outlined in this review highlight the significance of germline genomic variation in both susceptibility to toxicity and response to therapy. To date, only small numbers of clinically relevant, germline genetic biomarkers have been identified in children with cancer. Based on the available data (25, 26, 32, 33), larger prospective clinical trials of pharmacogenetic-based dosing of thiopurines and irinotecan are warranted to optimize the maximum effective dose of these agents based on TPMT and UGT1A1 genotype, respectively. Because pediatric populations have minimal comorbid conditions, they offer an ideal setting in which to study the pharmacogenomics of anticancer agents. In the developed world, most children have been diagnosed with cancer are entered into collaborative clinical trials, and the rise of both tumor and germline biobanks will ensure that materials are available for future pharmacogenomic investigations. Given the modest odds ratios of most genome-wide associations and the rarity of pediatric malignancies, international collaboration for future GWAS will likely be necessary.

Recent advances in our knowledge about the fundamental genomic alterations that are associated with variable tumor behavior and patient outcome has led to more precise prognostication and improved treatment stratification. Significant progress has also been made in the identification of specific molecular targets for novel therapeutics in some pediatric malignancies [reviewed in this edition of Clinical Cancer Research (1–4)]. To achieve our long-term goal of developing more effective, individualized therapy for all children with cancer, it will be important to define additional key pathways in pediatric tumors that can be exploited therapeutically. In addition, we need to improve our understanding of the heritable genetic factors that contribute to the response to and toxicity from chemotherapeutic agents in children.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: N. Pinto, S.L. Cohn
Writing, review, and/or revision of the manuscript: N. Pinto, S.L. Cohn, M.E. Dolan

Figure 3. Advantages of cell-based pharmacogenomic models. Data are publically available for lymphoblastoid cell lines with up to 10 million SNPs per cell line from the International HapMap Project and 1000 Genomes Project. Several laboratories have made miRNA and promoter methylation data for subsets of the HapMap cell lines publically available. Both miRNA and protein expression data can also be used for integrated analyses to assess how genotype affects sensitivity to pharmacologic phenotypes through effects on expression, epigenetics, or protein. These datasets (genotype, expression, and drug sensitivity) can be integrated to evaluate how genotype influences expression, and how genotype and expression influence sensitivity to a drug.
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