Precision Medicine in Pediatric Oncology: Translating Genomic Discoveries into Optimized Therapies

Thai Hoa Tran1,2, Avanthi Tayi Shah3,4, and Mignon L. Loh3,4

Abstract

Survival of children with cancers has dramatically improved over the past several decades. This success has been achieved through improvement of combined modalities in treatment approaches, intensification of cytotoxic chemotherapy for those with high-risk disease, and refinement of risk stratification incorporating novel biologic markers in addition to traditional clinical and histologic features. Advances in cancer genomics have shed important mechanistic insights on disease biology and have identified "driver" genomic alterations, which may represent actionable therapeutic targets. In this review, we will discuss how genomic discoveries are being translated from the bench into the clinic, resulting in the development of precision medicine trials for specific subtypes of pediatric hematologic malignancies, solid tumors, and brain tumors. Immunotherapeutic approaches will be discussed separately.

Introduction

Survival rates for children diagnosed with cancer have improved substantially over the past five decades. Today, long-term survival is expected for approximately 80% of children treated with contemporary therapies (1). These successes have occurred as a result of multicentered, randomized clinical trials that have largely tested the efficacy of dose intensification of conventional cytotoxic chemotherapy and the implementation of enhanced supportive care. Nevertheless, childhood cancer remains the leading cause of non-accident-related death in children, and for many cancers, further intensification of cytotoxic chemotherapy has failed to provide additional therapeutic benefit and has instead resulted in increased treatment-related mortality and undesirable long-term toxicity (2, 3). Therefore, innovative therapeutic approaches are urgently needed for patients with high-risk (HR) disease. Meanwhile, advances in cancer genomics have revolutionized the field of oncology and have become a crucial component in modern risk stratification algorithms and novel therapeutic avenues. The genomic and epigenetic landscapes of many childhood cancers have been recently elucidated and provide important insights into genetic alterations, signal transduction abnormalities, and epigenetic dysregulation, all of which may represent actionable therapeutic targets. In this review, we will discuss how genomic discoveries are being translated from the bench into the clinic, resulting in the development of precision medicine trials for specific subtypes of pediatric hematologic malignancies, solid tumors, and brain tumors. Immunotherapeutic approaches will be discussed separately.

Precision Medicine Therapeutics in Pediatric Hematologic Malignancies

Acute lymphoblastic leukemia

The treatment of Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ALL) represents the first paradigm of precision medicine principles in pediatric oncology. Comprising 3% of pediatric ALL, Ph+ALL harbors the canonical t(9;22)(q34;q11) translocation, resulting in the BCR–ABL1 oncoprotein. Ph+ALL was previously associated with a dismal outcome despite intensive multiagent chemotherapy and required hematopoietic stem cell transplantation (HSCT) in first remission (4). However, targeted inhibition of the ABL1 kinase domain with imatinib in combination with an HR ALL cytotoxic chemotherapy backbone significantly improved survival among children with Ph+ALL, such that HSCT is no longer universally recommended in first remission (4). Recent large-scale genomic profiling studies have identified a new subtype of HR B-lineage ALL (B-ALL) in which this paradigm of molecularly targeted therapy may be similarly efficacious. Philadelphia chromosome–like ALL (Ph-like ALL) is characterized by a gene expression profile (GEP) similar to that of Ph+ALL but lacks the hallmark BCR–ABL1 oncoprotein. Patients with Ph-like ALL who exhibit adverse clinical features face an exceptionally poor prognosis compared with patients with HR B-ALL without the Ph-like GEP when treated with modern chemotherapy regimens (5). The frequency of Ph-like ALL increases with age, ranging from 15% in children and adolescents to over 20% in adults, with a peak among young...
Recurrence of cytogenetic and molecular abnormalities in pediatric hematologic malignancies. The frequency of different genomic alterations of pediatric B-ALL, T-lineage ALL (T-ALL), and acute myeloid leukemia (AML) is depicted. Of note, the cumulative incidence does not add up to 100%, as more than one alteration can occur concomitantly.
DOT1L inhibitors) or histone deacetylation inhibitors (e.g., vorinostat, panobinostat, and bromodomain inhibitors) in combination with an ALL chemotherapy backbone will improve outcomes (14).

Unlike B-ALL, the heterogeneity of genetic alterations in T-lineage ALL (T-ALL) has precluded the identification of prognostic factors for risk stratification and the development of targeted therapeutic regimens. Nevertheless, genome-wide analyses have identified lesions that dysregulate key signaling pathways, some of which may represent novel therapeutic targets. For instance, the Notch signaling pathway is the most commonly deregulated pathway in T-ALL (15). Inhibition of Notch signaling by γ-secretase inhibitors (GI) that block the second cleavage of Notch1 and subsequent activation have been investigated in preclinical and early-phase studies. Unfortunately, the gastrointestinal toxicity associated with first-generation GSIs and their lack of efficacy in more common adult solid tumors have precluded further development in T-ALL trials. Alternative Notch-inhibiting strategies utilizing newer GSIs and anti-Notch1 immunotherapies are currently being investigated in adult trials (15). Furthermore, T-ALL is characterized by frequent activation of the PI3K/AKT/mTOR pathway, mostly as a result of inactivating mutations in PTEN. Inhibitors of this pathway have demonstrated preclinical efficacy, both alone and in combination with cytotoxic chemotherapy (16). Bortezomib, a proteasome inhibitor, is the only targeted therapy that has reached the threshold of testing in a first-line phase III trial for de novo pediatric T-ALL. The inclusion of bortezomib is based on the observation that constitutive activation of NF-κB often occurs in T-ALL blasts as a result of Notch or Akt activation. Furthermore, preclinical studies demonstrated that inhibition of NF-κB by bortezomib can enhance leukemia cell sensitivity to other traditional chemotherapeutic agents and may reverse steroid resistance, rendering it a promising target to incorporate into upfront clinical trials (15).

Despite survival rates approaching 90% in children with ALL who are treated with modern chemotherapy regimens, approximately 15% to 20% of patients still relapse, and outcomes following relapse are dismal (17). Genomic characterization of matched patient samples at diagnosis, remission, and relapse has deepened our understanding of the intertwined and complex interactions between clonal architecture, outgrowth and emergence of mutations, and mechanisms governing therapy resistance. Substantial genomic changes exist between diagnostic and relapsed ALL samples, illustrating the dynamic clonal evolution of leukemogenesis at recurrence (18). However, relapse-acquired mutations can often be detected at low levels at diagnosis, implying that ALL relapse can arise from the enrichment of rare, preexisting subclones (18). This finding further suggests a paradigm shift in which subclonal mutations may not only play a "passenger" role but rather, "drive" disease relapse. Recurrent genetic alterations associated with relapsed ALL include (i) activating somatic mutations in Ras pathway–related genes; (ii) somatic mutations in genes that confer chemoresistance, such as NT5C2, CREBBP, and PRPS1; and (iii) epigenetic dysregulation (19). Collectively, these data provide compelling rationale for the incorporation of MEK inhibitors and epigenetic modifiers in future precision medicine trials for relapsed ALL.

### Acute myeloid leukemia

Pediatric acute myeloid leukemia (AML) is a genetically heterogeneous disease with historically dismal outcomes, although the introduction of cytarabine and anthracycline-based intensive chemotherapy regimens now results in cure rates between 50% and 65% (20). Intensification of conventional chemotherapy has been maximized given the high frequency of treatment-related mortality in this patient population. Therefore, the development of novel therapeutic strategies relies on the knowledge derived from recent gene discovery studies. Approximately 75% of pediatric AML cases harbor genetic aberrations that may represent critical molecular targets. The most common cytogenetic abnormalities in childhood AML are the t(8;21)(q22;q22) and inv(16) (p13.1q22) translocations involving core-binding factor (CBF-AML), KMT2A-rearranged AML, and t(15;17)(q22;q21). Another

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**Table 1.** Precision medicine trials for different leukemia subtypes and their associated genomic alterations

<table>
<thead>
<tr>
<th>Leukemia subtype</th>
<th>Common alterations</th>
<th>Precision medicine approach</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph- ALL</td>
<td>BCR-ABL</td>
<td>Chemotherapy + imatinib</td>
<td>NCT01007474 – not yet recruiting</td>
</tr>
<tr>
<td>Ph-like ALL</td>
<td>ABL-class fusions (ABL1, ABL2, CSF1R, and PDGFRB), CRLF2 rearrangements and other JAK-STAT pathway lesions (JAK2 and EPOR rearrangements and/or IL7R and SH2B3 mutations)</td>
<td>Chemotherapy + dasatinib</td>
<td>NCT0283049 – recruiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT02420717 – recruiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT02723994 – recruiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT02420717 – recruiting</td>
</tr>
<tr>
<td>Infant ALL</td>
<td>KMT2A rearrangements associated with FLT3 overexpression and epigenetic dysregulation</td>
<td>Chemotherapy + azacitidine</td>
<td>NCT02828358 – recruiting</td>
</tr>
<tr>
<td>T-ALL</td>
<td>Activated NF-κB pathway alterations</td>
<td>Chemotherapy + bortezomib</td>
<td>NCT02953460 – recruiting</td>
</tr>
<tr>
<td>Relapsed ALL</td>
<td>PI3K/AKT/mTOR pathway alterations</td>
<td>Chemotherapy + everolimus</td>
<td>NCT01523997 – recruiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy + tamsirolimus</td>
<td>NCT01634917 – recruiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy + decitabine + vorinostat</td>
<td>NCT0183690 – completed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy + panobinostat</td>
<td>NCT01721546 – completed</td>
</tr>
<tr>
<td>AML</td>
<td>FLT3-ITD mutant</td>
<td>Chemotherapy + sorafenib</td>
<td>NCT01979896 – recruiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy + ATRA</td>
<td>NCT02393740 – recruiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ arsenic trioxide</td>
<td>NCT02680951 – recruiting</td>
</tr>
<tr>
<td>Relapsed AML with core-binding factor mutations</td>
<td>Chemotherapy + dasatinib</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: AML, acute myeloid leukemia.
major subgroup is defined by activating mutations in genes such as FLT3, KIT, and RAS, resulting in dysregulated signal transduction (21). The first precision medicine paradigm in AML incorporated all-trans retinoic acid to target the pathognomonic PML–RARα fusion of acute promyelocytic leukemia. The next-generation of AML-targeted therapy trials focused on the addition of FLT3 inhibitors to therapy regimens for patients with FLT3 mutations, which occur in 10% to 15% of pediatric AML and confer a poor prognosis (21). The current COG phase III trial for de novo AML, AAML1031, assesses the combinatorial effect of sorafenib, a multi-TKI with activity against FLT3, and conventional chemotherapy for FLT3-mutant AML. Other potentially targetable mutations that are now being investigated in early-phase clinical trials include those involving KIT and components of the Ras pathway (22). A phase I study of dasatinib has been completed in children with imatinib-resistant KIT mutations, whereas small-molecule Ras-pathway inhibitors have not yet reached clinical trials despite promising results in preclinical models (23). The distinct epigenetic profile of pediatric AML may further identify a subset of patients who may benefit from the addition of epigenetic modifiers. Recent studies testing the efficacy of hypomethylating agents, such as decitabine or azacitidine, in very HR or relapsed AML patients have shown early efficacy and may warrant further investigation (24).

**Precision Medicine Therapeutics in Pediatric Solid and Brain Tumors**

**Neuroblastoma**

The clinical presentation and survival rates of neuroblastoma patients vary greatly. Infants can present with tumors that regress spontaneously. Children with localized disease have >90% survival with minimal chemotherapy, whereas those with widely metastatic disease have only 40% to 50% survival despite receiving intensive multimodal regimens. Tumors in older children and adolescents are often chemoresistant, with a chronic, indolent course (25). The association between MYCN amplification and aggressive disease was first identified in the 1980s (26). Subsequently, DNA ploidy, gains of 17q, and deletions of 1p or 11q were identified as prognostic biomarkers (27, 28). Although some of these alterations have been incorporated into the International Neuroblastoma Risk Group (INRG) classification for risk group assignment (29), none of these findings have been translated into tailored therapies due to insufficient understanding of the oncogenes or tumor suppressors at these loci and their contribution to disease pathogenesis. Even for MYCN, whose role in tumorigenesis is well understood (30), there are yet to be targeted approaches. This is attributable to difficulties in designing a small molecule that can bind its helix-loop-helix structure (31). One approach is to target MYC, the heterodimerization partner of MYC, which is required for DNA binding. Drugs targeting the MYC:MAX interaction have demonstrated potential in vitro and in vivo (32). Another method is to target synthetic lethal interactions through CDK1, CDK2, or CHK1 inhibition (33–35). There are no active pediatric trials with CDK1 or CDK2 inhibitors, but the COG will be opening a phase I study with a CHK1 inhibitor. Drugs that target mTOR, PI3K, Aurora kinase, and Akt decrease MYCN stabilization, providing an alternative therapeutic strategy (32, 36, 37). Pediatric dosing for mTOR and PI3K/mTOR inhibitors is available, although their utility in neuroblastoma has not been fully investigated. Aurora kinase and Akt inhibitors are currently in pediatric clinical phase testing. A final approach to targeting MYCN is through bromodomain and extra terminal (BET) inhibition, as MYC family genes are targets of these chromatin readers. Studies of BET inhibitors in neuroblastoma cell lines and mouse models have demonstrated cytotoxicity (38); however, these drugs have yet to make it into clinical trials due to concerns for off-target toxicities.

Next-generation sequencing technologies have shed light on neuroblastoma heterogeneity at diagnosis and relapse (Fig. 2). Alterations most commonly occur in ALK at rates of 8% to 14% at diagnosis and 26% to 43% at relapse (39). Clinical trials with crizotinib, which is FDA approved for the treatment of ALK-rearranged non–small cell lung cancer, and early-phase clinical trials with next-generation ALK inhibitors have generated excitement among clinicians. Although RAS–MAPK alterations are rare at diagnosis, relapsed/refractory neuroblastoma specimens

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**Figure 2.**

Relative frequency of genomic alterations in neuroblastoma at diagnosis compared with relapse.
demonstrate enrichment for activating mutations in this pathway and susceptibility to MEK inhibition (40), offering another targeted approach that is in clinical testing. Interestingly, the CDK4/CDK6 cell cycle–regulatory pathway is implicated in neuroblastoma pathogenesis through CCND1 and CDK4 amplification or CDKN2A deletion, and the frequency of these alterations may be increased in the relapsed setting (39). In xenograft models, dual CDK4/CDK6 inhibition induced cell-cycle arrest and senescence (41). Furthermore, CDK4 inhibition sensitized MYCN-amplified neuroblastoma cells to doxorubicin-mediated death (42). Collectively, these discoveries underscore the potential for precision medicine to augment conventional therapies for neuroblastoma and highlight the need for biopsy at the time of relapse.

**Sarcomas**

Sarcomas comprise <15% of pediatric malignancies (43) but contribute largely to cancer-related morbidity and mortality. These patients desperately need new therapeutic strategies yet have seen few advances over the decades. Recent studies have described the genomic landscape of Ewing sarcoma, rhabdomyosarcoma, and osteosarcoma (44–48). They have shed light on sarcoma biology but have not yielded new treatments. This is due, in part, to the genomic profile of pediatric sarcomas, which is often characterized by gene rearrangements with a paucity of other alterations. Canonical translocations are ideal candidates for targeting, as they are drivers of oncogenesis only present in malignant cells. However, identifying tailored therapies has been challenging for at least two reasons. First, the chimeric protein is often not easily druggable. For example, the Ewing sarcoma translocation, EWS–FLI, does not form a fixed, three-dimensional structure under physiologic conditions, inhibiting inhibitor design (49). Only recently, a small-molecule, YK-4-279, was identified; it is able to block EWS–FLI protein interactions and results in cell cytotoxicity (50). It has transitioned to phase I testing in relapsed/refractory patients (51). Second, targeting EWS–FLI, as well as the alveolar rhabdomyosarcoma PAX–FOXO fusion, is difficult due to an absence of inherent enzymatic activity. Unlike most oncogenic rearrangements that result in kinase activation, these chimeric proteins activate and repress transcriptional activity of a wide array of genes, and reversal of these gene signatures is quite complicated. Trabectedin, a synthetic alkaloid, reversed the EWS–FLI signature in preclinical models; however, phase II testing did not demonstrate sufficient single-agent activity (51). Phase IIb combination testing is currently recruiting.

Incorporating precision medicine in the management of translocation-negative sarcomas has posed a challenge as well. Patients with fusion-negative rhabdomyosarcoma harbor alterations in multiple targetable pathways (Table 2). Unfortunately, these mutations occur at such a low rate that designing well-powered clinical trials can be problematic. Even in the complex and unstable osteosarcoma genome, which harbors multiple structural rearrangements and copy number changes, few targetable alterations are recurrent across multiple patients. Although we have gained new insights into sarcoma oncogenesis through genomic profiling, there are still many obstacles to leverage them into therapeutic strategies.

Despite these challenges, several candidates for targeted therapies have been identified. IGF-1R, PDGFR, VEGFR, and HER-2 have been observed to be overexpressed in osteosarcoma (52–55), and given their role in activating downstream signaling pathways that affect growth, cell proliferation, and survival, they pose an attractive target. However, clinical trials with the FDA-approved agents imatinib, sorafenib, and sunitinib did not induce significant responses in osteosarcoma (56–59). In addition, the anti–IGF-1R antibody cixutumumab, the anti-VEGF antibody bevacizumab, and the anti-HER2 antibody trastuzumab failed to demonstrate efficacy (60–62). Targeting the non–receptor tyrosine kinase Src sheds light on another therapeutic avenue for osteosarcoma patients, as it is implicated in the development of lung metastases through its activation of pathways necessary for cell survival, migration, adhesion, and invasion. In vitro, inhibition of Src resulted in decreased metastatic potential, but this was not replicated in vivo (63), highlighting that multiple pathways may be involved in the development of osteosarcoma metastases. A clinical trial for patients with recurrent osteosarcoma localized to the lung is currently underway. It is investigating the utility of saracatinib, an Src inhibitor, in patients who have had a complete surgical resection of their tumor. Ewing sarcomas have recurrent abnormalities in cohesin complex genes, including TP53 alterations, CDKN2A deletions, and STAG2 mutations (44–46). Synthetic lethality between cohesin complex mutations and PARP has been observed (64), thus prompting several trials investigating PARP inhibitors in combination with DNA-damaging agents in Ewing sarcoma.

### Table 2. Recurrent alterations in fusion-negative rhabdomyosarcomas are listed as copy number gains/losses or mutations with associated amino acid change when published

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR4</td>
<td>Mutation</td>
<td>6%–9%</td>
</tr>
<tr>
<td>IGF1R</td>
<td>Copy number gain</td>
<td>&lt;1%–2%</td>
</tr>
<tr>
<td>PDGFR</td>
<td>Mutation</td>
<td>1%</td>
</tr>
<tr>
<td>MET</td>
<td>Copy number gain</td>
<td>1%</td>
</tr>
<tr>
<td>BRAF</td>
<td>Mutation</td>
<td>&lt;1%–1%</td>
</tr>
<tr>
<td>IGF1R</td>
<td>Mutation</td>
<td>3%–4%</td>
</tr>
<tr>
<td>NFI</td>
<td>Mutation</td>
<td>5.4%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Mutation</td>
<td>5%–6%</td>
</tr>
<tr>
<td>CCND1</td>
<td>Mutation</td>
<td>1%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Mutation</td>
<td>2%</td>
</tr>
<tr>
<td>MDM2</td>
<td>Copy number gain</td>
<td>8%</td>
</tr>
<tr>
<td>TP53</td>
<td>Mutation</td>
<td>3.5%</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>Mutation</td>
<td>2%–3.3%</td>
</tr>
<tr>
<td>MYOD1</td>
<td>Mutation</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>BCR</td>
<td>Copy number loss</td>
<td>6%</td>
</tr>
<tr>
<td>FBXW7</td>
<td>Mutation</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

Improving the therapeutic paradigm for pediatric sarcomas is an urgent need, and ongoing clinical trials can be problematic. Even in the complex and unstable osteosarcoma genome, which harbors multiple structural rearrangements and copy number changes, few targetable alterations are recurrent across multiple patients. Although we have gained new insights into sarcoma oncogenesis through genomic profiling, there are still many obstacles to leverage them into therapeutic strategies.

**NOTE:** Of note, frequency reported is across fusion-negative and fusion-positive rhabdomyosarcomas. Data from Shukla et al. (93), Chen et al. (48), Shern et al. (47), and Kashi et al. (94).
Central nervous system tumors

Recent advances in central nervous system (CNS) tumor sequencing are shifting the field from a focus on histopathologic features to genetic identifiers. Rapid translation of molecular discoveries into informed therapies has gone hand-in-hand. Recently, genomic profiling elucidated four subgroups, based on molecular drivers of oncogenesis: WNT, SHH (Sonic Hedgehog), group 3, and group 4. These subgroups have been incorporated into the most recent 2016 World Health Organization (WHO) classification, which takes into account molecular markers in addition to pathologic features (65), redefining the framework in which CNS tumors were previously diagnosed. The WNT group harbors somatic mutations in the CTNNB1 gene or, in more rare instances, germline mutations in the APC tumor suppressor gene (66). These alterations upregulate the WNT pathway, resulting in tumorigenesis. No targeted therapies exist for these patients, but because their overall survival approaches 90% (67), future studies may examine therapy deintensification. The SHH group contains aberrations in the SHH pathway, most commonly in PTCH1 but also in SMO, SUFU, and GLI2 (68). A phase 1 study of the FDA-approved SMO inhibitor vismodegib demonstrated activity in SHH medulloblastoma (69) and may offer a molecular-guided therapy for this subset of patients. It is important to note that tumors with abnormalities in SUFU or GLI2 are downstream of SMO and, thus, resistant to vismodegib (70). Unfortunately, less is known about the specific genetic drivers in group 3 and group 4. Group 3 tumors have the worst prognosis and a high frequency of copy number abnormalities. They often have high MYC expression, and a subset is MYCN amplified. Group 4 tumors also harbor copy number alterations and often have amplifications in CDK6 and MYCN. As described above, there are challenges to targeting MYC, but bromodomain inhibition has shown promise in preclinical models of medulloblastoma with MYCN amplification (71). Palbociclib, a dual CDK4/CDK6 inhibitor is currently in phase 1 testing.

Molecular features have also been integrated in the most recent WHO classification of posterior fossa and supratentorial ependymomas given the wide histopathologic variation across tumors, which results in lack of concordance even among experts (65, 72). Posterior fossa ependymomas have been subdivided into two groups. Group A tumors lack recurrent genetic alterations but have increased methylation of CpG islands, resulting in transcriptional silencing of targets of polyclomic repressive complex 2. In vitro, drugs targeting the polyclomic repressive complex 2 and DNA-demethylating agents impair proliferation of ependymoma cells (73). Group B tumors have multiple chromosomal aberrations, but none that are amenable to targeting (74). Supratentorial ependymomas generally harbor two classes of gene rearrangements. The majority contains a fusion of c11orf95 and RELA, whereas the remainder have fusions involving the transcriptional coactivator YAP1 (75). Unfortunately, no targeted therapies exist for these chimeric proteins. Because 75% percent of ependymoma expresses aberrant ERBB2 and ERBB4 signaling (76), laptatinib, an ERBB inhibitor, has been the subject of active clinical investigation (77). It has failed to demonstrate efficacy, but this may reflect the need for higher levels of laptatinib in vivo and, thus, still holds promise.

Pediatric low-grade gliomas are characterized by numerous mutations and copy number alterations, including somatic alterations in BRAF. The most common alterations are translocations in BRAF, which generate fusion proteins that result in loss of BRAF regulation and activation of the MAP kinase pathway. The BRAFV600E mutation, which leads to constitutive activation of BRAF, is also found in low-grade gliomas. These findings have led to several clinical trials examining BRAF inhibitors in the V600E-mutated patients. BRAF inhibitors are contraindicated in patients with BRAF fusions, as it results in feedback loop–mediated upregulation of the pathway and accelerated tumor growth. Accordingly, MAP kinase inhibitors are under investigation in this cohort of patients. As our understanding of the molecular oncogenesis of CNS tumors continues to grow, we are likely to identify new therapeutic strategies to enhance our current management of these patients.

In light of these novel therapeutic avenues, the COG is developing the pediatric counterpart of the adult NCI-MATCH trial to enroll children and adolescents with relapsed/refractory solid tumors, CNS tumors, and lymphomas (Fig. 3). In addition to offering molecular-targeted therapy for these patients, the trial will also provide a rich source of genomic data for future discovery.

Precision Medicine in Pediatric Oncology: New Horizons and Future Challenges

In addition to suggesting novel therapeutic targets, gene discovery studies enhance other aspects of the precision medicine algorithm, including cancer surveillance, assessment of inherited susceptibility to therapy-related toxicity, and treatment response monitoring. The Pediatric Cancer Genome Project identified that 8.5% of children and adolescents with cancer had germline mutations in cancer predisposition genes in which family history failed to predict the presence of an underlying predisposition syndrome in most patients (78). The most commonly affected genes were TP53, APC, BRCA2, NFI, PMS2, RB1, and RUNX1. In addition to several previously well-described predisposition syndromes, such as Li-Fraumeni syndrome, new associations have been observed between germline mutations of TP53, PMS2, and RET mutations with Ewing sarcoma; APC and SDHB mutations with neuroblastoma; and a diverse range of mutations in APC, VHL, CDH1, PTCH1, and SDHA with leukemia (78). Knowledge of these inherited predispositions has major implications on direct patient care and on disease surveillance as well as genetic counseling for patients and their families. Furthermore, several genome-wide association studies have identified polymorphisms in genes that predict susceptibility to common chemotherapy-related complications, such as polymorphisms in TPMT (79) and NUDT15, which are associated with abnormal thiopeurine metabolism, resulting in severe myelosuppression (80); polymorphisms in GRIAl associated with asparaginase allergy (81), whereas those in CPA2 are associated with asparaginase-induced pancreatitis (82); variants in ACPI, BMP7, and PROX1-AS1 that predispose to glucocorticoid-induced osteonecrosis (83, 84); polymorphisms in HASS predisposing to anthracycline cardiomyopathy (85); polymorphisms in CEP72 associated with vincristine neuropathy (86); and variants in SLCO1B1 involved in methotrexate clearance (87). Given that genetic testing for TMPT status to inform adjustments in mercaptopurine dosage has already become standard practice in ALL, one could envision the implementation of a tailored pharmacogenomic panel relevant to a specific chemotherapy regimen to individualize therapy based on genetic risk factors that predict host toxicities. Finally, advances in the technologies to detect cancer cells have paved innovative ways...
to measure treatment response and ultimately predict risk of relapse. Childhood leukemia treatment response measured by minimal residual disease (MRD) has been identified as a powerful independent prognostic factor (88). It has traditionally been measured by flow cytometry or other molecular-based techniques. However, sensitive next-generation sequencing–based MRD monitoring is being tested prospectively in several pediatric oncology consortia for clinical relevance (89). Although MRD measurement has revolutionized the management of patients with leukemia, similar ultrasensitive biomarkers are essentially nonexistent for our solid tumor patients. Recently, several adult studies demonstrated that detection of circulating tumor DNA (ctDNA) in the plasma can predict relapse earlier than can be seen on standard imaging studies. Very few investigations of the utility of ctDNA in pediatric solid tumors exist; however, preliminary results using droplet digital PCR and next-generation sequencing are encouraging (90–92). In parallel, several challenges emerge from the new era of precision medicine, including intratumoral genomic heterogeneity that makes it difficult to distinguish driver from passenger mutations, lack of sustained response resulting from the emergence of acquired drug-resistant mutations and escape pathways, and incorporation of genomic sequencing technologies into pragmatic, real-time, cost-effective clinical workflows for treatment decision making. In addition, new ethical dilemmas have arisen due to the incidental detection of inherited susceptibility to cancer predisposition syndromes. Genomics-driven targeted therapies will require a strong collaboration between basic scientists, molecular pathologists, bioinformaticians, and oncologists to develop robust clinical trials to address these issues in an effort to further improve patient survival.

**Conclusions**

Advances in cancer genomics have deepened our understanding of the disease biology, uncovered actionable genomic alterations, and offered unique opportunities for precision medicine approaches. Several molecular-targeted therapy trials are currently under way in the hopes of balancing survival and toxicity for these HR patient populations. However, this exciting era of tailored therapy also opens up new challenges. The next generation of translational trials will aim: (i) to determine the optimal combination between novel therapeutic agents and conventional cytotoxic drugs; (ii) to investigate the underlying mechanisms governing therapy resistance as the emergence of drug-resistant
mutations and compensatory feedback pathways can arise; and (iii) to harness international collaboration to design statistically powered trials for rare, HR, genomically defined entities. Hence, precision medicine illustrates a novel treatment paradigm to improve outcomes for children with cancer in this modern era of multi-omics.

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No potential conflicts of interest were disclosed.

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References


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