Progress in precision therapy in pediatric oncology

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Abstract

Purpose of review: The fields of precision medicine and cancer genomics in pediatric oncology are rapidly evolving. Novel diagnostic tools are critical in refining cancer diagnoses, stratifying patient risk, and informing treatment decisions. This review is timely and relevant as it discusses advantages and drawbacks of common molecular profiling techniques and highlights novel platforms which may address select limitations. We discuss recent publications demonstrating utility of large-scale molecular profiling and feasibility and logistics of matching targeted therapies to patients.

Recent findings: We describe the increased accessibility of next-generation sequencing, complementary profiling methods, and strategies to guide treatment decisions. We describe curation and sharing of large genomic datasets and novel mechanisms to obtain matched targeted therapies. Importantly, we discuss relevant publications in distinct disease domains that support indications for evidence-based precision therapy. Lastly, we introduce the incremental analyses that can be obtained via whole genome and transcriptome sequencing.

Summary: Here we highlight high-yield clinical scenarios of precision medicine approaches and identify the ongoing challenges including universally defining clinical actionability, optimizing trial design to account for molecular heterogeneity while acknowledging limitations in patient accrual, expanding access to molecularly-targeted therapies, and validating new tools and technology to aid in precision medicine therapeutic approaches.

Keywords

precision oncology; molecular profiling; targeted therapy

INTRODUCTION

Background on Utility of NGS Testing in Pediatric Oncology

Over the last several decades, the outcomes of patients with pediatric malignancies have improved dramatically with overall survival rates exceeding 85%. However, a subset of patients with rare and aggressive tumors remains that requires novel therapies and treatment

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strategies. The rapidly evolving fields of cancer genomics and precision medicine have been instrumental in refining cancer diagnoses with molecular sub-classifications, stratifying patient risk, and informing treatment decisions. Over the last 5 to 10 years, the utilization of broad next-generation sequencing (NGS)- based targeted gene panels has evolved from limited research concentrated at large academic centers to widely available standard of care. These assays evaluate several hundred clinically relevant and/or actionable genes implicated in the development and behavior of tumors and capture genomic aberrations including: mutations (single nucleotide variants; SNVs), amplifications, deletions, a subset of common rearrangements/fusions, as well as specific gene signatures such as tumor mutational burden (TMB) and microsatellite instability (MSI). Select DNA-based NGS panels are interpreted in the context of a matched normal control which enhances the sensitivity of somatic variant calling by accounting for germline single nucleotide polymorphisms that can be subtracted from the tumor sequencing results. The evaluation of matched germline and tumor sequencing has also broadened our understanding of the spectrum of germline predisposition syndromes in pediatric oncology.(1*)

One major limitation has been that current commercially available NGS assays were developed primarily to identify biomarkers of adult cancer subtypes. Compared to adult malignancies, pediatric tumors have a lower mutational burden with an enrichment of structural variants, which are not uniformly captured with standard sequencing methodology. Several complementary profiling efforts now exist to supplement DNA -based panels, including dedicated RNA NGS (e.g. Archer FusionPlex), identifying fusions with greater sensitivity.(2) In addition, DNA methylation profiling, which evaluates the epigenetic modification of gene expression, has led advances in molecular classification of pediatric brain tumors due to fast turn-around time and small tissue requirements.(3)

Many academic centers and cooperative groups have sought to evaluate the role of NGS-based panels with respect to feasibility and clinical utility, and reported rates of clinical actionability have ranged from 4–78%.(4–7*) These discrepant results are attributable in part to selection bias and the variable definitions and tiered classifications of clinically actionable genomic variants. Whether the results of NGS panels can improve survival of pediatric cancer patients remains an open question to be addressed by large, multinational clinical studies.(8)

Collaborative Initiatives to Improve Access and Curate Data

As genomic profiling of pediatric tumors becomes more mainstream, several national initiatives, including the National Cancer Institute's (NCI) Childhood Cancer Data Initiative, have been developed to collect and annotate genomic and clinical data pertaining to pediatric cancer with the goal of creating tools to visualize and analyze these large datasets. The Molecular Characterization Initiative was launched in 2022 in collaboration with the Children's Oncology Group (COG) to provide free comprehensive genomic profiling (whole exome sequencing, RNA-NGS, and methylation) to pediatric patients with newly diagnosed central nervous system tumors, soft tissue sarcoma or other rare tumors, with plans to extend to other histologies.(9) Similarly, Project GENIE (AACR), an international cancer registry developed to share data among 19 leading cancer centers, has been developed to aggregate

clinical data, genomic data, and survival outcomes.(10) The hope is that these collaborations will leverage large data sets to improve understanding of the biology of rare molecularly defined cohorts and generate novel hypotheses to treat pediatric cancers.

Mechanisms to Obtain Novel Therapies

While a foundational principle of precision medicine is selecting an appropriate drug to match a relevant biomarker and disease-type, an equally important consideration is patient access to the therapy. In the absence of an FDA-approved indication, the preferred path to access is enrollment onto a biomarker-driven clinical trial wherein enrolled subjects are treated homogeneously, objective response and toxicity data are collected uniformly, and response assessments are evaluated in the context of a predetermined statistical plan. These factors permit generalizable conclusions about safety and efficacy of a given biomarker-drug pairing. Several platforms exist using a master molecular screening protocol to support a "basket" (histology-agnostic) or "umbrella" (within histology) trial,(11) the most notable of which are the NCI-COG MATCH(7*, 12–14) and AcSé-ESMART studies,(15–18) both demonstrating the feasibility of collaborative, multi-institutional consortium-based precision oncology studies. These trials allow diverse histologies with comparable genomic alterations to be analyzed together in a single cohort to efficiently evaluate efficacy signals of novel therapies in rare tumor subsets. Molecularly enriched cohorts are also being evaluated in smaller, single- or multi-center industry sponsored studies and investigator-initiated trials. Often limited by trial-based requirements for centralized testing and therefore, tissue availability, more recent efforts are allowing inclusion onto molecularly defined cohorts using test results from any CLIA-certified lab (NCT03155620). An ongoing challenge, is that while there are several validated systems to approach oncogenicity and predefined levels of evidence for targetability (for example: OncoKB(19)), it not feasible for trials to be completely comprehensive in their molecularly-annotated inclusion criteria.

In cases where a clinical trial is unavailable or not feasible, off-label use of FDA-approved targeted therapy remains a viable option. However, sufficient pre-clinical or clinical evidence may be lacking in a pediatric histology to provide a compelling rationale for insurance or health agency approval. A single-patient use (SPU)(20) request through the FDA's expanded-access program can be helpful in these cases or circumstances where the agent is not yet approved for any indication. Unfortunately, major limitations of SPU applications are the time and resources required to seek approval and the adherence to regulatory reporting requirements which are a significant administrative burden. Moreover, such off-label "n-of-one" patient experiences rarely make it into the literature, especially when negative, representing a profound loss of potentially minable or generalizable data. The Secured Access to innovative medicines for CHildren with cAncer (SACHA) initiative was developed by the French Society of Pediatric Oncology to address this issue. This pilot effort confirms the feasibility of a prospective observational study and registry of safety and efficacy data from pediatric patients with relapsed/refractory cancers for whom off-label or compassionate use of anti-cancer therapies were prescribed.(21) Plans to expand this initiative through the Innovative Therapies for Children with Cancer (ITCC) consortium are ongoing by developing a "SACHA International Project" in collaborating countries.

Major Precision Oncology Updates by Disease Category

Targeted therapy applications vary significantly by disease type, stage and molecular aberration classification (SNV, fusion, amplification, etc). Below are some of the most recent examples of the successful deployment of precision oncology for pediatric cancer.

Pediatric Leukemia—After the landmark successes of targeting the canonical *BCR/ABL* fusion with single-agent tyrosine kinase inhibitor (TKI) therapy in chronic myelogenous leukemia (CML), new clinical challenges have emerged including understanding long-term toxicities and assessing the safety of stopping TKIs during major molecular remission (to be assessed in an ongoing study, NCT03817398). Furthermore, response to single-agent molecularly targeted therapy has extended beyond CML as evidenced by recently reported results demonstrating the efficacy of the MEK inhibitor trametinib in patients with relapsed/refractory juvenile myelomonocytic leukemia (JMML) with detectable Ras mutation, yielding an overall response rate of 44% (4/9 patients) with a tolerable side effect profile. (22) This study not only demonstrates the success of studying an extremely rare patient population, but also provides the background to evaluate trametinib in combination with conventional upfront therapy in newly diagnosed patients with JMML. This approach was used to study sorafenib in pediatric patients with high allelic ratio FLT3/ITD (>0.4) acute myeloid leukemia (AML) who were treated with standard of care (SOC) chemotherapy with or without sorafenib. Outcomes were more favorable in the sorafenib plus chemotherapy group and patients treated with chemotherapy alone had approximately double the amount of events (death, relapse, refractory disease).(23)

Ongoing efforts are in place to integrate the molecular and immunophenotypic profiling of high-risk pediatric leukemias and identification of trials for matched targeted therapies. These initiatives include a collaboration between the Leukemia & Lymphoma Society (LLS), NCI, and COG (Pediatric Acute Leukemia, PedAL, initiative and European correlate, EupAL) as well as GEARBOx (Genomic Eligibility Algorithm at Relapse for Better Outcomes) which was developed by the University of Chicago's Pediatric Cancer Data Commons team to match patients with relapsed AML to appropriate therapeutic trials.(24)

Pediatric CNS Tumors—Recent research has shown that the vast majority of pediatric low grade gliomas (pLGGs) have alterations that activate the RAS-MAP kinase pathway. (25, 26) The most common alterations are loss of neurofibromin in the context of patients with neurofibromatosis type 1 (NF1), and either *BRAF*^{V600E} mutation, or fusion (*BRAF-KIAA1549*)/tandem duplication of *BRAF* in non-NF1-related pLGG.(27, 28*, 29) These seminal discoveries prompted precision oncology trials targeting the RAS-MAP kinase pathway with BRAF inhibitors (BRAFi) (first generation BRAF monomer inhibitors, and second generation BRAF dimer inhibitors) or MEK inhibitors (MEKi) (functioning downstream of RAF) (30, 31). A recent phase 2 study reported promising results in patients with recurrent/refractory BRAF (ORR 36%) or NF1 altered pLGG (ORR 40%) treated with selumetinib, an oral MEKi.(30) Consequently, two randomized clinical trials were launched to compare the ORR and functional outcomes for newly diagnosed pLGGs treated upfront with either selumetinib or SOC chemotherapy in NF1 and non-NF1 pLGGs (NCT03871257, NCT04166409). Analogous to MEKi, tovorafenib, a second generation BRAFi (blocks

BRAF dimers and causes less paradoxical activation) demonstrated impressive ORR in recurrent/refractory *BRAF* fusion driven pLGGs (NCT04775485), and a global phase 3 randomized trial comparing tovorafenib vs SOC chemotherapy for newly diagnosed patients is planned.

For adult and pediatric patients with solid tumors that have a *BRAF* V600E mutation, dabrafenib (BRAFi) and trametinib (MEKi) in combination received tumor agnostic approval based on impressive results noted in the phase 2 ROAR trial(32), NCI-MATCH 'basket' trial(33**), and a pediatric phase1/2 study (34). Preliminary results of a randomized phase II study (dabrafenib/trametinib versus chemotherapy) for patients with *BRAF* V600E mutant pLGGs supports the use of combined BRAFi and MEKi molecular targeted therapy for front line treatment in lieu of chemotherapy.(35)

Infant-type high-grade gliomas (HGG), which are molecularly distinct from HGGs occurring in older children, are increasingly recognized as driven by fusions involving *ALK*, *ROS, MET* and *NTRK*.(36) These kinase fusion-positive tumors have better outcomes and respond to targeted therapy (i.e. entrectinib (*ALK/ROS/TRK*)(37) and larotrectinib (*TRK*) (38)), strongly supporting a change in diagnostic practice and management.(36)

Methylation profiling of embryonal CNS tumors can be a powerful adjunct to diagnosis, subgroup assignment, risk stratification, and treatment assignment, particularly in clinical trials for medulloblastoma and CNS primitive neuroectodermal tumors (PNETs). For example, methylation demonstrated prior misclassification of discrepant molecular entities (*H3G34* mutant glioblastomas and *ZFTA*-fused ependymomas) as PNETs and defined previously unrecognized subgroups with distinctive pathological features.(39) Subsequently, WHO removed CNS PNETs as a diagnostic entity and a clinical trial was closed prematurely (NCT00392327) due to concern that important signals might be lost in a uniformly treated molecularly heterogenous group of tumors.(40) Post hoc molecular analysis demonstrated that 75% of histologically diagnosed CNS PNETs could be reclassified into different molecular entities after DNA methylation profiling.(40) Methylation and comprehensive genomic profiling has now been incorporated into the evolving management of medulloblastoma and CNS PNETs with the goals of reducing therapy and avoiding radiation for molecularly defined low risk groups with good outcomes, and identifying high-risk groups in need of novel treatment approaches.(41–43)

Pediatric Solid Tumors (non-CNS)—The landmark successes of single-agent, targeted therapy for extracranial solid tumors thus far have been largely attributable to using a TKI to target a constitutively activated tyrosine kinase receptor in the setting of a canonical gene rearrangement.(8) Examples of these gene-fusion/drug pairs include: *NTRK*/larotrectinib,(44) *ALK*/crizotinib,(45) and *RET*/selpercatinib,(46) as well as various next-generation inhibitors of the same class. Unfortunately, when extending the use of TKIs to tumors characterized by other genomic aberrations (amplification, non-*BRAF* V600 SNV) in the same target gene, responses have been infrequent. For example, in patients with neuroblastoma harboring activating *ALK* SNVs, ORR for single agent crizotinib and lorlatinib were 15%(47) and 18%(48), respectively. This contrasts with the efficacy of ALK

inhibition in fusion driven tumors such as anaplastic large cell lymphoma and inflammatory myofibroblastic tumors where response rates up to ~90% have been reported.(45)

This phenomenon is likely attributable to the genomic complexity of most high-grade lesions (e.g., osteosarcoma, embryonal rhabdomyosarcoma, neuroblastoma) which harbor multiple driver alterations and is further exemplified by the early results of the pediatric MATCH trial (NCT03155620).(7*) In the first published study, 21 patients with eligible MAPK pathway alterations (*NF1, KRAS, NRAS, HRAS, BRAF*V600E) including high-grade histologies such as HGG, rhabdomyosarcoma, adenocarcinoma, and MPNST were enrolled on Arm E, a phase 2 study of selumetinib (NCT03213691), and no objective responses were seen.(13) For this reason, histology-specific clinical trials focusing on adding targeted inhibition to conventional chemotherapy with the goal of augmenting anti-tumor activity are being pursued, such as the addition of ALKi therapy in patients with newly diagnosed, *ALK*-mutant neuroblastoma (NCT03126916). In addition, an ongoing effort through National Clinical Trials Network (NCTN), the ECOG-ACRIN-NCI-ComboMATCH, will test combinations of targeted therapies for which there is strong biologic and preclinical rationale for synergistic activity. The goal of multi-agent therapy is to overcome drug resistance and augment response compared to single-agent therapy.

The use of targeted inhibitors in solid tumors is expanding beyond TKIs to include those that target the DNA damage response pathway with the goal of targeting potential tumor-specific therapeutic vulnerabilities that can be identified via NGS testing.(49) For example, elimusertib, a highly specific ATR inhibitor, is in phase 1/2 testing (NCT05071209) for two histology specific cohorts characterized by replication stress (Ewing sarcoma and PAX3/FOXO1 fusion-positive rhabdomyosarcoma) and for a biomarker-driven, histology-agnostic cohort for patients with tumors harboring loss of function mutations in *ATM, ATRX, BRCA1, BRCA2, CDK12, CHEK1, CHEK2, FANCA, MSH2, MRE11, PALB2, PARP1, POLD1, RAD51,* and XRCC2 with the goal of achieving synthetic lethality.

Future Directions and Precision Oncology Beyond Genomics

Cancer whole genome and transcriptome sequencing (cWGTS) has started to gain traction as a research assay that can comprehensively assess the full spectrum of germline and somatically acquired mutations and gene expression profiles in pediatric malignancies. This methodology has potential clinical utility to better capture novel genomic variants and other unexpected mechanisms of oncogenesis or treatment resistance.(50*–55*) Rather than relying on estimates of TMB and MSI derived by NGS panel testing, cWGTS directly quantifies genome-wide mutational burden across all variant classes, potentially identifying patients susceptible to immune checkpoint inhibitors. cWGTS can also denote various genomic signatures, such as that associated with BRCAness, potentially enriching for patients likely to respond to DNA damage repair agents. cWGTS, while promising, has limitations; broad-scale implementation is challenged by high costs, strict tissue requirements, and complexity of laboratory and analytical workflows. Currently, cWGTS exists as a promising research tool, but is not yet a tractable replacement for CLIA-certified NGS panels. It is also clear that precision oncology should encompass far more than understanding the DNA blueprint of a cancer cell. Efforts are underway to characterize

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the complexities of the tumor microenvironment, tumoral immune infiltrate, and proteome/surfaceome, in parallel, and to intentionally exploit discovered therapeutic vulnerabilities.

Challenges and Conclusions:

As universal access to tumor NGS is realized, significant questions in the field of precision medicine remain. Still lacking are consensus definitions of "clinically actionable" genomic aberrations and streamlined analyses of federated data to help understand the true impact of molecularly targeted therapies on overall and event-free survival. It is critically important to incorporate new, emerging datasets (such as RNAseq and proteomics) and leverage novel computer algorithms and artificial intelligence to guide treatment decisions. Furthermore, significant efforts must be directed at the strategic optimization of targeted therapy including timing of administration. Soon, it may be possible to reduce or even eliminate chemotherapy for specific sub-groups of low-grade tumors susceptible to targeted therapy like pLGG. For high grade/high risk tumors, evidence does not currently favor replacing cytotoxic chemotherapy with targeted therapies, however it is important to continue to evaluate how precision molecular diagnostics, risk stratification, and targeted therapies meaningfully impact patient outcomes by improving survival and minimizing acute and late toxicity.

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Key Points:

- Next generation sequencing is becoming a widely utilized tool to aid in diagnostic classification and identification of rational therapeutic targets.

- Significant advances have been made in pediatric oncology with regard to the safety, feasibility, and efficacy of treating select low grade tumors with targeted therapeutics.

- Novel and complementary profiling methods are critical to enhance the utility of existing clinical tools.