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Precision oncology: A primer for pediatric surgeons from the APSA cancer committee

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ABSTRACT

Although most children with cancer can be cured of their disease, a subset of patients with adverse tumor types or biological features, and those with relapsed or refractory disease have significantly worse prognosis. Furthermore, current cytotoxic therapy is associated with significant late effects. Precision oncology, using molecular therapeutics targeted against unique genetic features of the patient's tumor, offers the potential to transform the multimodal therapy for these patients. Potentiated by advances in sequencing technology and molecular therapeutic development, and accelerated by large-scale multi-institutional basket trials, the field of pediatric precision oncology has entered the mainstream. These novel therapeutics have important implications for surgical decision making, as well as pre- and postoperative care. This review summarizes the current state of precision medicine in pediatric oncology including the active North American and European precision oncology clinical trials.

Level of evidence: Treatment study
Level V.

Contents

Abbreviations: ALL, Acute lymphoid leukemia; ALK, Anaplastic lymphoma kinase; COG, Children's Oncology Group; EGFR, Epidermal growth factor receptor; ESMART, European Proof of Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumor; FDA, Food and Drug Administration; GM-CSF, Granulocyte-macrophage colony-stimulating factor; HR, Hazard ratio; IL-2, Interleukin-2; mTOR, Mammalian target of rapamycin; MATCH, Molecular analysis for therapy choice; NCI, National Cancer Institute; NGS, Next Generation Sequencing; NSCLC, Non-small-cell lung cancer; PD-1, Programmed cell death receptor 1; RR, Relative risk; SCT, Stem cell transplant; TKI, Tyrosine kinase inhibitor; VEGF, Vascular endothelial growth factor; WES, Whole exome sequencing.

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Cancer is the leading disease-related cause of death in children and adolescents. [1] In 2018, an estimated 10,590 children aged 0–14 developed cancer and 1180 will die from their disease. While more than 80% of children with cancer will be long-term survivors, the prognosis is much worse for subsets of patients with adverse tumor type, stage, and/or biology. [1,2] Children with relapsed and refractory tumors are a population in particular need of novel therapeutics in order to improve survival. For instance, children with high risk neuroblastoma have a >50% risk of relapse; and those with relapsed or refractory disease have <10% chance of long-term survival. [3,4] Similarly, in Wilms tumor, the risk of relapse is low (15%), but the 4-year survival is still markedly diminished (50%) in relapsed patients. [5]

The need for novel therapeutic agents is also driven by the long-term complications associated with current therapies, including chemotherapy, radiation and surgical management. By age 45, 95% of patients treated for childhood cancer developed a chronic health condition, including a serious or disabling condition in 80% of survivors. [6] Serious late effects may manifest in childhood, including poor growth, precocious puberty or delayed/arrested puberty, and neurocognitive disorders. [6] Furthermore, children treated for childhood cancer are at risk for secondary malignancies, including skin, central nervous system, leukemia, breast, and thyroid cancers which occur in more than 15% of patients. [6,7] The development of more targeted interventions has the potential to improve survival while minimizing morbidity, including late effects owing to the nontargeted nature of current treatment regimens.

As the use of novel therapeutics targeted towards actionable mutations increases, it is imperative for pediatric surgeons to understand these agents and their implications for perioperative management. For example, some targeted therapies have been associated with serious wound complications, which can increase the morbidity of major resections and possibly delay reconstructions or adjuvant therapy. Furthermore, some therapies have been associated with surgical complications such as gastrointestinal perforation. As experience with targeted therapies in children with cancer increases, pediatric surgeons remain critical in the multidisciplinary care of these patients. In the future, targeted therapies may even change surgical paradigms including the timing and/or goals of surgical excision.

1. What is precision oncology?

Precision medicine is defined by the National Cancer Institute (NCI) as, “an approach to patient care that allows physicians to select treatments that are most likely to be effective based on a genetic understanding of the patient's disease.” Although applicable to a wide variety of medical disciplines, the relationship between genetic mutations and tumorigenesis makes oncology a prime focus for precision medicine. In the field of oncology, targeted cancer therapies refer broadly to agents which interact with specific molecular targets unique to a particular malignancy. These targeted agents are distinguished from traditional cytotoxic chemotherapy. When these targeted therapies are applied to a subset of patients based on specific genetic alterations in their tumors, the term precision oncology is most appropriate. While still in its early stages, the field of precision oncology has progressed rapidly in the past decade. [8,9]

1.1. Genomic organization

The genome is defined as an organism's collection of DNA, a double stranded helix of paired nucleotides which encodes every protein produced by the organism. The human genome consists of approximately 3 billion DNA base pairs, folded about intracellular proteins called histones, organized on 23 paired chromosomes (as well as a small complement of mitochondrial DNA) and stored in the cell's nucleus. Only 1–2% of DNA codes for expressed protein, the exome, which will be transcribed into RNA and ultimately translated into protein. Although we typically think of the genome on an organism level, each cell contains its individual copy of DNA allowing for the occurrence of somatic evolution/mutation and the development of most malignancies.

Alterations in the exome account for many genetically acquired diseases. Genomic alterations include single nucleotide variations (SNVs) in individual base pairs. These may be synonymous (in which a single nucleotide switch produces a sequence which encodes the same amino acid as the reference genome) or nonsynonymous (in which the change in nucleotide encodes an alternate amino acid). Other variant types include insertions and deletions (“indels”) in which a section of DNA is either elongated or missing over a few sequential bases often resulting in shifts in the reading frame that lead to truncated or misfolded proteins.

Genomic alterations are not limited to substitution of base pairs; entire regions of the genome may be deleted or duplicated resulting in copy number alterations. Alleles can be deleted and duplicated, resulting in a “loss of heterozygosity” (LOH). Genes may be cut out of their typical position and stuck into another place in the genome, resulting in a fusion gene product.

In addition to genetic variations, epigenetic modifications affect cellular gene expression without being directly encoded in the DNA sequence. DNA methylation and histone binding (acetylation, methylation, and ubiquitination) are common epigenetic modifiers which are known to affect the transcription and expression of genes. [10] Epigenetics are responsible for the tremendous diversity in cell structure and function seen throughout a given organism.

1.2. Identifying targets for precision oncology

Precision oncology is predicated on the availability of rapid, cost-effective and reproducible genetic sequencing. The origins of modern genomic analysis can be traced to the development of Sanger sequencing in the 1970s. [11] “Next Generation” Sequencing (NGS) technologies drastically increased the scale of sequencing pursuits, producing millions to billions of sequencing reads per run, allowing the characterization of entire genomes, transcriptomes (RNA products of the genome), and epigenomes (the epigenetic modifications of the genome). (Fig. 1) One major advantage of these large-scale methods in cancer genomics is the ability to study the entire genome simultaneously, eliminating the bias introduced by interrogating only selected subsets of previously implicated cancer genes. In the modern era, NGS technologies follow the basic principle of massively parallel, cyclic interrogation of short, amplified DNA sequences and have become the first level of genomic interrogation. [12] Intensive computational resources are then required to align these short reads to unique locations within the human reference genome. Short read-sequence does pose problems for sequence

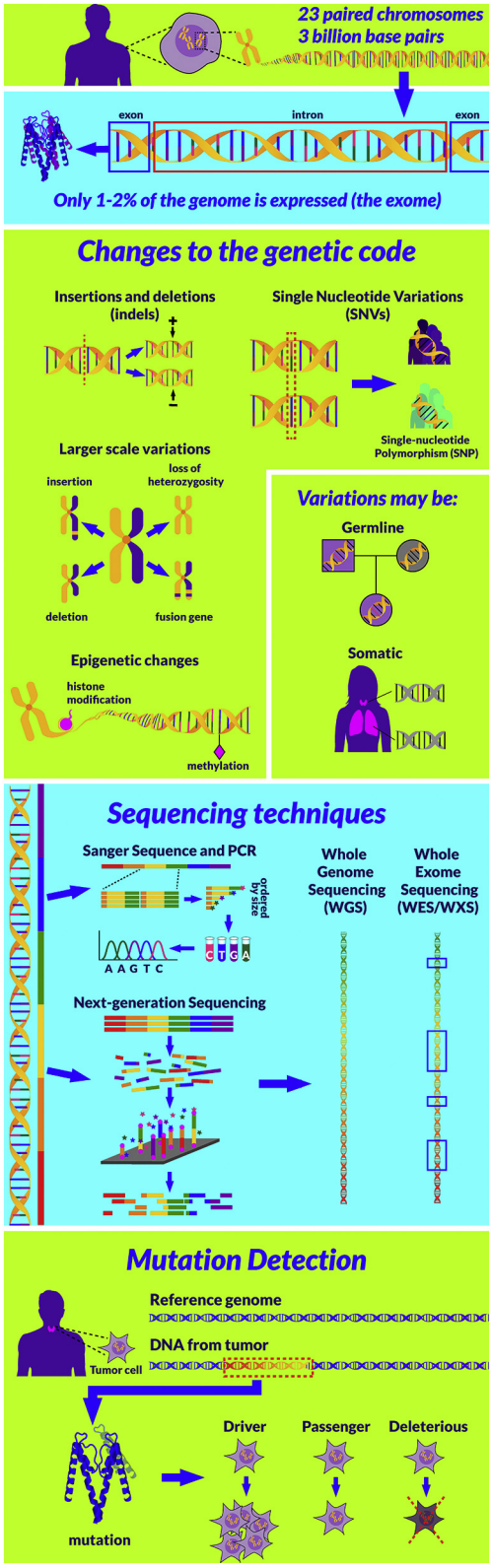

Fig. 1. Schematic of the genetic basis of precision medicine techniques.

assembly, particularly in segments with a lot of variability or structural variation. Multiple overlapping reads (known globally as the "coverage depth") are typically employed to compensate for uncertainty owing to sequence quality and base accuracy. [13,14]

NGS studies treat tumors as genetically heterogeneous populations of individual clones accumulating mutations during the process of tumorigenesis and tumor progression. Any mutation within a tumor may therefore play one of three roles: 1) it may be a "driver mutation" which is causally implicated in tumorigenesis and confers a selective growth advantage; 2) it may be a "passenger mutation" which is selectively neutral or; 3) it may be deleterious for subsequent tumorigenesis and will be eventually purged. [15] Evidence from the Cancer Genome Atlas suggests there are a limited number of highly recurrent "hotspot" driver mutations and a far larger number of mutations which affect only a minority of a given cancer subtype. Identifying which of the non-"hotspot" mutations are clinically or biologically relevant is a critical but nontrivial task given the enormous number of mutations identified through NGS. This task is typically allocated to one of a number of publicly available algorithms which may annotate any given variant along a scale from "probably benign" to "probably deleterious."

Although sequencing of the whole genome (WGS) is technically feasible and is frequently encountered in the research setting, both the cost and computational burden of WGS make it impractical for routine clinical use. Instead, whole exome sequencing and targeted sequencing are more routinely encountered in clinical practice. These techniques target the exome (all protein-coding regions of the genome) or a prespecified set of cancer-associated genes. In addition to lowering cost and accelerating processing time, curated gene panels (commercial examples of which include Oncomine Dx, Thyroseq, TruSight, and FoundationOne CDx) have the advantage of allowing increased depth of coverage over a gene, increasing the true positives of rare variants and decreasing the amount of tissue required for analysis. However, gene panels have the disadvantage of limiting tumor genomic analysis to a limited number of genes and may miss important mutations or mutational signatures which might be identified if the entire exome were sequenced.

In theory, most precision oncology therapies are primarily targeted against somatic (tumor-specific) mutations. The additional clinical benefit of germline sequencing to confirm whether mutations within the tumor are de novo is debated. Germline analysis increases sequencing requirements and costs without necessarily identifying additional targets for molecular therapies. Jones, et al. analyzed whole exomes and somatic (cancer) genes by NGS in 815 patients with 15 cancer types. [16] Using matched somatic-to-germline sequencing comparison, 77% of patients had somatic alterations in genes associated with established or investigational therapies (33%) and/or drugs in current clinical trials (67%). Also, 3% of patients who were thought to have sporadic cancers had germline alterations in cancer predisposing genes. Sequencing of the tumor alone would not have identified these germline alterations in cancer predisposition genes. Moreover, identification of germline risk alleles has significant bearing on genetic counseling for family members who may also be at risk.

1.3. Referral for sequencing evaluation

In contrast to adult tumors, those in children are more likely due to inherited or sporadic genetic mutations, rather than environmental factors. Precision genomic analysis thus has increased application in the pediatric population. [17,18] Although potentially beneficial for all pediatric tumor types – newly diagnosed, refractory and relapsed – the clinical utility of genetic analysis is greatest in some specific scenarios. Pediatric tumors with undifferentiated histology may benefit from genetic analysis for further tumor characterization and to guide therapy [19] Additionally, patients with relapsed and/or refractory tumors may benefit from sequencing to identify potential second-line treatment agents for those who have progressed despite standard therapy. Rates of actionable mutations may be higher in relapsed disease, as was the case for *ALK* mutations in patients with relapsed neuroblastoma. [20] Lastly, tumor sequencing may help to identify those with cancer predisposition syndrome, to guide follow-up evaluation and counseling of presymptomatic family members. [18,21] In one study 8.5% of children with cancer were found to have a genetic predisposition, and this rate has been increasing as NGS-methods have facilitated identification.

[22] For patients with tumors that are associated with cancer predisposition syndromes there are many tools that practitioners can use to guide whether or not they should refer their patient for germline genetic testing. [23,24]

1.4. Established applications of precision oncology

Imatinib (Gleevec®) is a tyrosine kinase inhibitor (TKI) which targets the ABL1 kinase domain of the BCR-ABL1 gene on the Philadelphia chromosome (t(9;22)(q34;q11) (Ph+). It was approved by the Food and Drug Administration (FDA) in 2001 for chronic myeloid leukemia and significantly improved survival for these patients. [25] The discovery of imatinib heralded the beginning of the precision oncology era both for adults and children. For children with Ph + acute lymphoid leukemia (3% of pediatric ALL) imatinib improved survival and reduced the need for hematopoietic stem cell transplant. Five-year disease free survival in patients treated with chemotherapy plus imatinib was 71%, compared with 64% for related donor stem cell transplant (SCT) and 63% for unrelated donor SCT. [26]

In the nearly 20 years since imatinib was first released, multiple other targeted molecular therapies have demonstrated efficacy and have been approved by the FDA for use in adults. One of the most well known examples is trastuzumab (Herceptin®), a monoclonal antibody that inhibits human epidermal growth factor receptor protein (HER2) in HER2 amplified breast cancer, which was approved in 1998. In a phase III trial, the addition of trastuzumab to traditional chemotherapy improved median survival from 20.3 to 25.4 months for women with advanced metastatic disease (RR for death 0.76, $p = 0.025$). [27] Another well-established example of precision oncology in adults is vemurafenib (Zelbora®) for cutaneous melanoma with BRAF V600E mutations, which was approved in 2011. This drug inhibits the ATP-binding domain of the mutant BRAF. In a phase III trial of vemurafenib vs. dacarbazine, vemurafenib improved 6 month overall survival from 64% to 84% (HR for death 0.37, $p < 0.001$). [28] Lastly, erlotinib (Tarceva®) was approved by the FDA in 2004 for patients with non-small-cell lung cancer (NSCLC). Erlotinib inhibits the epidermal growth factor receptor (EGFR) tyrosine kinase. Although originally approved for all patients with NSCLC, the FDA revised its approval in 2013 to only the subset of patients with NSCLC harboring an EGFR mutation. For this drug, phase III trial of erlotinib vs. placebo for patients who failed traditional chemotherapy demonstrated a median survival of 6.7 months vs. 4.7 months (HR for death 0.7, $p < 0.001$). [29] As these examples demonstrate, the field of precision oncology typically yields incremental gains rather than monumental survival benefits.

Several targeted therapies have demonstrated efficacy in phase III pediatric trials and the FDA has approved some for the treatment of children with cancer. Dinutuximab (Unituxin®) is an FDA-approved (2015) anti-GD2 antibody that induces cell-mediated and complement-dependent cytotoxicity against GD2-expressing tumor cells including neuroblastoma. In a phase III study, immunotherapy with dinutuximab (ch14.18) combined with interleukin-2 (IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF) significantly improved event free (66% vs. 46%) and overall (86% vs. 75%) survival in children with high-risk neuroblastoma. [30] This agent has now become part of post-consolidation therapy in all treatment arms of the current high-risk neuroblastoma study (ANBL1531). In 2018 the FDA approved iobenguane I-131 (AZEDRA®) for use in pediatric patients with metastatic pheochromocytoma or paraganglioma. This drug is taken up by the norepinephrine transmitter and the resulting radioactive decay of I-131 causes cell death and tumor necrosis. This approval was based on Study IB12B, yet to be published, which demonstrated improved tumor response and reduction of antihypertensive medications. [31] Likewise the anti-CD20 monoclonal antibody rituximab (Rituxan®) has demonstrated efficacy in pediatric non-Hodgkin's lymphoma by inducing B-cell lysis. Although not yet FDA-approved for this indication, there have been multiple trials demonstrating improved response rate and increased survival compared to traditional chemotherapy. [32] [[33].

While several targeted therapies have established track records of safety and efficacy in children with cancer, the number of well-established applications of true precision medicine is more limited. Crizotinib (Xalkori®) has demonstrated high response rates in children with anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma and ALK-positive inflammatory myofibroblastic tumor. [34] ALK is a receptor tyrosine kinase, and oncogenic mutations (including chromosomal translocations leading to a fusion protein, activating point mutations, and gene amplification) promote cell cycle progression, migration and evasion of apoptosis. Utilization of this agent in the subset of children with these identified oncogenic mutations is now well established and was approved by the FDA in 2018. This agent has also demonstrated efficacy in children who have neuroblastoma with an ALK mutation and is being further investigated in the current high-risk study. The anti-CD33 antibody gemtuzumab ozogamicin (Mylotarg®) was approved in 2017 for the treatment of children with CD33-positive acute myeloid leukemia. Approval in pediatric use was based on adult phase III trials that demonstrated improved overall survival, decreased risk of relapse and a dose adjustment with a lower toxicity profile. [35,36] Additionally, the TKI dasatinib (Sprycel®) is approved for pediatric patients with Ph + chronic myeloid leukemia who have failed treatment with imatinib. In a phase II trial that led to the FDA approval, the cytogenetic response rate and progression free survival were significantly improved. [37] Finally, the FDA recently approved the anti-programmed cell death receptor 1 (PD-1) protein monoclonal antibody pembrolizumab (Keytruda®) for use in adult and pediatric cancers with microsatellite instability-high or mismatch repair deficient solid tumors. This approval was based on combined data from five adult clinical trials that showed improved response rate regardless of the primary tumor site. [38] This was the first targeted anticancer therapy approved by the FDA for use based solely on biomarker status, rather than specific sites.

Epigenetic dysregulation is a feature of most hematological malignancies and increasingly recognized as playing a role in solid tumors. The FDA recognizes a growing number of histone deacetylase (HDAC) and DNA methyltransferase (DNMT) inhibitors including vorinostat (2006), belinostat (2015), azacytidine (2004) and decitabine (2006). [10] More recently the isocitrate dehydrogenase (IDH) inhibitors enasidenib (2017) and ivosidenib (2018) have been approved, and multiple other epigenetic modulators are in development. Azacitidine and decitabine are approved for elderly patients with acute myeloid leukemia (AML) unable to tolerate standard chemotherapy. Belinostat and vorinostat are FDA approved for treatment of cutaneous T-cell lymphoma. [39] IDH hotspot mutations are common in AML, glioma, and cholangiocarcinoma and IDH inhibitors are the source of several phase II and phase III studies. [40,41] While epigenetic modulators have not been widely introduced into treatment paradigms for pediatric tumors, there is growing interest in their use both in hematologic malignancies as well as in brain tumors in which epigenetic modulation appears to be a driving oncogenic event. [42]

1.4.1. Precision oncology in children: the Pediatric MATCH Trial

The NCI-COG Pediatric MATCH Trial (MATCH = molecular analysis for therapy choice) is a collaboration between the NCI and Children's Oncology Group (COG) in which children with refractory or recurrent tumors are matched with targeted therapies correlating to specific molecular changes in their tumors (COG APEC1621). The primary aim of the trial is to determine whether the targeted therapies produce an objective response. Secondary aims include estimating progression free survival and obtaining information about tolerability of these drugs in children and adolescents. All drugs used have at least an adult recommended phase 2 dose and have shown some activity against tumors with a particular genetic alteration. This is a basket trial, which includes

patients with a certain genetic mutation regardless of the site in the body or underlying histology.

As of the end of 2018 there are ten arms of the Pediatric MATCH, with plans to add more as the study continues. The targeted drugs work through various mechanisms including tyrosine kinase receptors, growth factor receptors, transcription factors and DNA damage repair mechanisms. The goals of these therapies are to halt unregulated cell growth, encourage tumor suppressor genes, promote apoptosis and restore appropriate DNA repair mechanisms (Table 1).

1.4.2. Precision oncology in children: the European AcSe´-ESMART Trial

In addition to the major basket trial underway in the US, a European proof-of-concept study is also in progress. Unlike the MATCH trial, the sequencing in this European study is being performed on multiple different panels, and a "tumor board" discussion is being utilized to assign patients to treatment arms. Patient sequencing data are reviewed for a match in one of the European Proof of Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors (ESMART) trial arms or other targeted clinical trials. The primary outcome measures of this ongoing trial are objective tumor response and time to progression. [43] Patient enrollment began in August 2016 and preliminary data were presented at the 2017 American Association for Cancer Research annual meeting. Patients between the ages of 0 and 18 years with recurrent or refractory malignancies had their tumor sequenced by whole exome and RNA sequencing after biopsy or resection. From the preliminary data, 174 patients were included with 104 completely analyzed and discussed. Seventy-six percent of the patients with complete analysis had at least one "actionable" target found. Twenty-one patients were enrolled in the EMSART trial and 5 were registered in other clinical trials with targeted agents. [44] The AcSé-ESMART has the potential to discover new targeted therapy agents while utilizing conventional chemotherapy.

1.5. Rates of actionable mutations

While studies in adults have demonstrated that most patients with metastatic cancer have clinically informative results from gene sequencing, far fewer children who undergo NGS are found to have a targetable mutation. A single institution study in 2015 screened 104 patients with relapsed cancer and 46% were found to have actionable mutations that affected their cancer management. Actionable mutations were found in 54% of those with hematological malignancies compared to 43% of those with solid tumors. [45] These results were similar to another single institution study in 2016 that enrolled 101 patients. Potentially targetable genomic alterations were found in 38% of patients but only acted upon in 6 (16%). Of those with hematological malignancies 47% had targetable alterations compared to only 32% of those with solid tumors. [46] While these early studies demonstrated that there is a potential role of NGS to identify clinically actionable alterations, there are currently a multitude of barriers and limited identifiable targets.

1.6. Resistance to targeted therapy

As our clinical experience with targeted therapies grows, so too does our awareness of the problem of resistance to targeted therapy. Most targeted therapies relevant to pediatric patients with solid tumors target tumor-promoting mechanisms in the following biological processes: cell survival (mutations in EGFR, PIK3CA, BRAF, PTEN, MYC, etc.), cell fate (mutations in APC, NOTCH, AR, GATA2, KLF4, etc.), and genomic stability (mutations in TP53, ATM, BRCA1, BRCA2, etc.). However, even highly effective targeted therapies to one or more of these processes are subject to development of resistance within the tumor, rendering them only transiently effective. Since most tumors are extremely heterogenous, harboring multiple subpopulations of cells with distinct mutations, the response to a single targeted agent will vary within the tumor itself. Also, the microenvironment surrounding the tumor, especially at distant metastatic sites, can influence response to therapy. Specifically, resistance to targeted therapy occurs through one of four major mechanisms [47]:

1) Mutations within the target — for example, short lived responses to imatinib in some patients result from mutations in BCR-ABL which interfere with binding of imatinib to its target [48]
2) Reactivation of a targeted pathway either upstream or downstream from the target — for example, upregulation of BRAF can reduce the efficacy of MEK inhibitors [49]
3) Activation of alternative pathways — for example, activation of the parallel MAPK signaling pathways that reduce the efficacy of mTOR inhibitors targeting PI3K [50,51]
4) Cross-talk within the tumor microenvironment — for example, cell–cell and cell–extracellular matrix interactions have been shown to influence resistance to PI3K/mTOR inhibitors [52]

Recognition of the development of resistance in targeted therapeutic agents is in guiding future research and therapeutic regimens. Targeted therapies may need to be combined or given sequentially to overcome reactivation or hyperstimulation of alternative pathways. Also, pediatric surgeons must recognize that tumor heterogeneity may require new strategies for tumor sampling — including biopsies separated regionally or temporally as well as biopsies of distant metastases which may have distinct tumor microenvironments. [47]

1.7. Surgical considerations

As the field of precision oncology continues to develop rapidly by bringing targeted therapies to more children, pediatric surgeons should be aware of timing considerations and potential complications associated with these therapies. Most pediatric surgeons will encounter targeted therapies as part of a multimodality treatment strategy, which also may include cytotoxic chemotherapy, radiation therapy, and surgery. Some classes of targeted therapies are associated with major wound complications when given in the neoadjuvant setting; therefore, communication and coordination with medical oncologists and radiation oncologists are imperative. In a phase II study of the antiangiogenic vascular endothelial growth factor (VEGF) receptor inhibitor bevacizumab in treatment of soft tissue sarcomas, the associated rate of major postoperative wound complications was 25%. [53] Although significant, this rate is comparable to the overall wound complication rate of 30% in extremity soft tissue sarcoma resections following neoadjuvant chemotherapy and radiation. [32- [54] Whether the severity of wound complications (dehiscence versus superficial infection or seroma) differs with these agents has not been well studied.

Additionally, there is a lack of clinical data on when these drugs should be held for a planned surgery, and thus no evidence-based guidelines exist. There are some recommendations for specific TKIs that range from 24 h to 28 days depending on the drug's half-life. [55] In a phase II/III clinical trial including the TKI pazopanib for treatment of nonrhabdomyosarcoma soft tissue sarcomas, the COG included expanded wound complication data collection and advised holding the preoperative (for one week) and postoperative (for two weeks) doses of pazopanib (ARST1321). The concern for wound healing, however, must be balanced against the oncologic implications of prolonged therapy cessation.

Wound healing complications have also been associated with mammalian target of rapamycin (mTOR) inhibitors, especially in the setting of transplant. In a meta-analysis of surgical procedures on transplant patients on mTOR inhibitors, dose reduction was the most effective way to prevent wound complications. [56] Introducing a bundle of care for surgical patients on mTOR inhibitor therapy, including preoperative dose reduction when possible, use of preoperative antibiotics, and use of closed suction drains as appropriate has been associated with a reduction in wound

Table 1
Pediatric MATCH Trial Arms (APEC1621).

Genetic Target	Mechanism of Action (drug target)	Molecular function of drug target	Pediatric malignancies typically harboring this mutation	Drug under investigation
(APEC1621A) *NTRK1, NTRK2, NTRK3*	Inhibitor of pan-TRK (tropomyosin receptor kinase), which is a tyrosine kinase receptor	Common ligands of TRK receptors are neurotrophins that activate signaling cascades including phospholipase C (PLC), Ras/MAPK pathway and PI3 which leads to nervous system growth	Gliomas, mesoblastic nephroma, infantile fibrosarcoma	Larotrectinib (LOXO-101) – po BID
(APEC1621B) *FGFR1, FGFR2, FGFR3, FGFR4*	Inhibitor of FGFR (fibroblast growth factor receptor), which is a tyrosine kinase receptor	Regulates cell growth via phosphorylation events, pathways include Phospholipase C/PI3K/Akt, Ras, protein kinase C, IP3 Ca/Calmodulin	Glioblastoma, rhabdomyosarcoma	Erdafitinib (JNJ-42756493) – po QD
(APEC1621C) *SMARCB1, SMARA4, EZH2*	Inhibitor of EZH2 (enhancer of zeste homolog 2), which is a histone-lysine N-methyl transferase enzyme	EZH2 is the catalytic subunit of the only human histone methyltransferase that can methylate H3K27; hyper trimethylation of H3K27 is transcriptionally repressive, silencing tumor suppressor genes	NHL (follicular lymphoma and diffuse large B cell lymphoma), INI-1 deficient tumors, carcinomas, cutaneous melanoma, gliomas, medulloblastomas, ependymoma	Tazemetostat (EPZ-6438) – po BID
(APEC1621D) *TSC1, TSC2, NF1, NF2, PTEN, PIK3R1, MTOR, PIK3CA*	Inhibitor of PI3K (phosphionositide 3-kinase), which is a kinase Inhibitor of mTOR (mammalian target of rapamycin), which activates pro-growth and antiapoptotic pathways	Phosphorylates pathway that promotes cellular growth and proliferation over differentiation in stem cells	Osteosarcoma, embryonal rhabdomyosarcoma, diffuse intrinsic pontine glioma	LY3023414 – po BID
(APEC1621E) *NF1, NRAS, HRAS, KRAS, ARAF, BRAF, MAP2K1, GNA11, GNAQ*	Inhibitor of MEK (mitogen activated protein kinase), which is a kinase	MEK is involved in the MAPK pathway (RAS–RAF–MEK–ERK pathway) that leads to activation of transcription factors that leads to cell growth and division	Hematological and lymphoid malignancies, rhabdomyosarcoma, low grade glioma, glioblastoma multiforme, neuroblastoma, malignant peripheral nerve sheath tumors, melanoma	Selumetinib (AZD6244 hydrogen sulfate) – po BID
(APEC1621F) *ALK, ROS1*	Inhibitor of ALK (anaplastic lymphoma kinase), which is a tyrosine kinase receptor	Activates many downstream signaling pathways that mediate growth and cell cycle progression including PI3-Kinase-Akt, Jak/STAT3, Ras/MAPK	Neuroblastoma, NSCLC, anaplastic thyroid carcinoma, anaplastic large cell lymphoma, inflammatory myofibroblastic tumor, rhabdomyosarcoma, melanoma, CNS tumors, ovarian, breast, Ewing's, retinoblastoma	Ensartinib (X-396) – po QD; second generation; (more potent than first generation Crizotinib)
(APEC1621G) *BRAF*	Inhibitor of BRAF, which is a protein kinase	BRAF is involved in the MAPK pathway (RAS–RAF–MEK–ERK pathway) that leads to activation of transcription factors that leads to cell growth and division	Hematological and lymphoid malignancies, rhabdomyosarcoma, low grade glioma, glioblastoma multiforme, neuroblastoma, malignant peripheral nerve sheath tumors, melanoma	Vemurafenib – po BID
(APEC1621H) *BRCA1, BRCA2, ATM, RAD51C, RAD51D*	Inhibitor of PARP (poly ADP-ribose polymerase), which is a family of proteins in the nucleus involved in DNA repair	Function in DNA damage repair via base excision repair in single-stranded DNA by signaling other DNA repair enzymes	Wilm's, ovarian, breast	Olaparib (Lynparza®)– po BID
(APEC1621I) *CDK4, CDK6, CCND1, CCND2, CCND3*	Inhibitor of CDK 4/6 (cyclin-dependent serine–threonine kinase), which are kinases	CKD4/6 combine to form a complex that phosphorylates pRB tumor suppressor protein that releases transcription factors to progress from G1 to S phase in cell proliferation	Malignant rhabdoid tumors, neuroblastoma, supratentorial PNET, medulloblastoma, glioblastoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma	Palbociclib (Ibrance®)– po QD
(J) *NF1, MAPK1, BRAF, NRAS, HRAS, KRAS, ARAF, MAP2K1, GNA11, GNAQ*	Inhibitor of ERK 1/2 (extracellular signal-related kinase) [also known as MAPK, mitogen-activated protein kinase], which are kinases	ERK1/2 are involved in the MAPK pathway (RAS–RAF–MEK–ERK pathway) that leads to activation of transcription factors that leads to cell growth and division	Hematological and lymphoid cancers, rhabdomyosarcoma, low grade glioma, glioblastoma multiforme, neuroblastoma, malignant peripheral nerve sheath tumors, melanoma	Ulixertinib (BVD-523FB) – po BID

complications in adult kidney transplant recipients. [57] Similar strategies may be explored for pediatric surgical oncology patients as more data emerge on specific wound healing complications in the perioperative period.

Additionally, pediatric surgeons should be aware of potential complications of targeted therapeutics that may not be operative-related but nonetheless require surgical management. Bevacizumab has a well-documented association with gastrointestinal perforation. [58] More recently, colonic perforations were documented in phase II trials of the multikinase inhibitor regorafenib in a study which included adolescent patients with metastatic osteosarcoma. In fact, perforations associated with targeted therapeutics have been reported at various locations throughout the gastrointestinal tract from the duodenal bulb to the rectum. [59–61] TKIs, including pazopanib, have been implicated in the development of spontaneous pneumothorax, but a case–control series showed no evidence of increased risk for patients with metastatic disease to the chest. [62] Understanding the complications of targeted therapies even in nonsurgical pediatric oncology patients is essential since having a high index of suspicion for gastrointestinal perforation may speed diagnosis and management.

1.8. Future implications for the pediatric surgeon

Precision medicine is beginning to transform the field of medical oncology in pediatrics. The implications for the field of pediatric surgical oncology are also exciting. Precision medicine has the potential to impact all aspects of surgical care — from preoperative counseling to surgical decision-making and postoperative management. Targeted therapies may allow for reduced surgical invasiveness with subsequent reduction in surgical morbidity, but may also contribute to their own set

of morbidity including wound and anastomotic complications. In the short term, surgeons and interventional radiologists may be called upon more frequently to biopsy newly diagnosed, refractory or relapsed tumors in order to assess for potential therapeutic targets. In the longer term, progress in the field may allow for reliable noninvasive "liquid biopsy" — a biopsy using biologic fluid (blood, cerebrospinal fluid, urine, etc) to detect and analyze circulating tumor DNA for diagnosis, to assess treatment response, and determine actionable mutations.

2. Conclusion

The ultimate goal of precision oncology is to provide a customized treatment regimen for every child with cancer that maximizes survival while minimizing both early and long-term morbidity. A key aspect of this paradigm is the utilization of molecular therapies targeted against a patient's unique genetic features. Large basket trials underway in North America and Europe will help determine the rates of actionable mutations and the objective response to targeted therapies. In the future, genetic analysis may also allow for reliable molecular diagnosis with "liquid biopsy" and/or assessment of treatment response and "minimal residual disease," (signs of residual disease detectable only through molecular analysis), through sequencing of circulating tumor DNA. This paradigm may allow for elevation or reduction of multimodal therapy for each individual patient.

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