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Rare tumors: Opportunities and challenges from the Children's Oncology Group perspective

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ABSTRACT

While all childhood cancers are rare, tumors that are particularly infrequent or underrepresented within pediatrics are studied under the umbrella of the Children's Oncology Group Rare Tumor committee, divided into the Retinoblastoma and Infrequent Tumor subcommittees. The Infrequent Tumor subcommittee has traditionally included an emphasis on globally rare tumors such as adrenocortical carcinoma, nasopharyngeal carcinoma, or those tumors that are rare in young children, despite being common in adolescents and young adults, such as colorectal carcinoma, thyroid carcinoma, and melanoma. Pleuropulmonary blastoma, gonadal stromal tumors, pancreatic tumors including pancreatoblastoma, gastrointestinal stromal tumor, nonmelanoma skin cancers, neuroendocrine tumors, and desmoplastic small round cell tumors, as well as other carcinomas are also included under the heading of the Children's Oncology Group Rare Tumor committee. While substantial challenges exist

Abbreviations: AYA, Adolescent and Young Adult; ACC, Adrenocortical Carcinoma; ACT, Adrenocortical Tumor; COG, Children's Oncology Group; CNS, Central Nervous System; CRC, Colorectal Carcinoma; ctDNA, Circulating Tumor Deoxyribonucleic Acid; DTC, Differentiated Thyroid Carcinoma; FOLFOX, Leucovorin calcium (Folinic acid), Fluorouracil, Oxaliplatin; MCI, Molecular Characterization Initiative; NCI, National Cancer Institute; NIH CCDI, National Institutes of Health Childhood Cancer Data Initiative; NPC, Nasopharyngeal Carcinoma; PCDC, Pediatric Cancer Data Commons; PPB, Pleuropulmonary Blastoma; PTC, Papillary Thyroid Carcinoma; RPLND, Retroperitoneal Lymph Node Dissection; RNA, Ribonucleic Acid; TKI, Tyrosine Kinase Inhibition; US, United States.

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in rare cancers, inclusion and global collaboration remain key priorities to ensure high quality research to advance care.

1. Background

Rare diseases are defined by the Orphan Drug Act as those that impact fewer than 200,000 people per year in the United States (US). If impact is defined solely by the frequency of diagnosis, then all pediatric cancers qualify as rare diseases including acute lymphoblastic leukemia and pediatric gliomas. Within pediatric cancer however, there are subsets of tumors which are particularly infrequent and/or understudied. These infrequent tumors are the focus of the Children's Oncology Group (COG) Rare Tumor Committee.

The COG is an international consortium of more than 200 institutions across North America, Australia, New Zealand and Saudi Arabia which includes more than 10,000 members, primarily pediatric oncologists, radiologists, surgeons, interventionalists, pathologists, advanced practice practitioners, pharmacists, and research specialists. Broadly speaking, COG is divided into 12 disease-specific committees (e.g., acute lymphoblastic leukemia, renal tumors, soft tissue sarcomas, rare tumors etc.), as well as 13 discipline-based committees (e.g., adolescent and young adult (AYA), nursing, surgery, radiology etc.), and 6 domains (e.g., cancer care delivery, cancer control and supportive care, developmental therapeutics, epidemiology, outcomes-survivorship and stem cell transplantation).

The Rare Tumor Committee within COG is divided into the Retinoblastoma and Infrequent Tumor subcommittees. The Infrequent Tumor subcommittee uses a practical definition of which tumors are included, encompassing all extracranial solid tumors that do not fall within another COG disease committee. It has traditionally focused on rare tumors such as adrenocortical carcinoma (ACC) and nasopharyngeal carcinoma (NPC) or those tumors that are rare in young children, even if common in adolescents and young adults, such colorectal carcinoma (CRC), thyroid carcinoma, and melanoma. Pleuropulmonary blastoma (PPB), gonadal stromal tumors, pancreatic tumors including pancreatoblastoma, gastrointestinal stromal tumor, nonmelanoma skin cancers, neuroendocrine tumors and desmoplastic round cell tumors as well as other carcinomas are also included under the purview of the Rare Tumor committee (Table 1). Ongoing committee initiatives are focused on NPC, PPB, ACC, CRC, melanoma and retinoblastoma.

1.1. Nasopharyngeal carcinoma (NPC)

NPC is a rare tumor seen in fewer than 1 in 100,000 individuals and more commonly diagnosed outside the US. While outcomes in both the US and Europe have been excellent for pediatric NPC, the burden of acute and long term toxicities remains high and includes severe lifelong effects related to radiation therapy [1–3]. The next proposed COG study, ARAR2221, aims to test the addition of immunotherapy to chemoradiotherapy, with a goal to reduce radiation dose in an effort to decrease toxicity while also preserving outcomes. Given the rarity of this tumor, we recognize the need for international collaboration and remain in discussions with multiple cooperative groups regarding both protocol strategies and data harmonization. While there are some differences in treatment regimens between the proposed COG trial (ARAR2221) and the German Pediatric Oncology Group GPOH open study (GPOH-NPC-22), the current COG protocol is strategically designed to be run in parallel to European efforts with plans for concordant data collection and future comparison efforts.

Table 1
List of tumors which are included in rare tumor group.

Eligible Rare Tumor Diagnoses:
Thyroid Carcinoma
Colorectal Carcinoma
Gastrointestinal Stromal Tumors
Adrenocortical Carcinoma
Nasopharyngeal Carcinoma
Retinoblastoma
Melanoma
Desmoplastic Small Round Cell Tumors
Pancreatoblastoma
Neuroendocrine Tumors
Pleuropulmonary Blastoma
Gonadal Stromal Tumors
Any other carcinomas

1.2. Pleuropulmonary blastoma (PPB)

PPB is a rare thoracic neoplasm seen primarily in very young children. Nearly all clinically significant PPB is diagnosed in children under the age of 7 years. Type I PPB is a purely cystic, generally air-filled lesion diagnosed at a median age of 7 months [4]. Type I PPB may progress to Type II (mixed cystic and solid), or Type III (purely solid) PPB diagnosed at a median age of 35 and 39 months respectively [5]. While Type I PPB is associated with a favorable prognosis, further standardization of the indications for administration of chemotherapy is needed. For Types II and III PPB, outcomes remain suboptimal. The proposed prospective clinical trial (ARAR2331) will include administration of camptothecins as window therapy and during consolidation and maintenance therapy to reduce the risk of recurrence and central nervous system (CNS) metastatic disease in children with advanced PPB. This trial will also test the ability of circulating tumor deoxyribonucleic acid (ctDNA) to serve as a prognostic biomarker in Types I, II and III PPB.

1.3. Colorectal carcinoma (CRC)

While common in adults, CRC remains infrequent in the pediatric population, with an approximate annual incidence of 5 per 1 million individuals in the US under age 20 [6]. Children and adolescents with CRC have a greater tendency towards unfavorable histologic diagnoses and stage 3 and 4 disease, as well as poorer 5-year survival rates when compared with early onset adult patients [7]. Despite this, pediatric specific molecular profiling, treatment, and outcome data is lacking, with the majority of pediatric patients treated using adult protocols [7]. Recently, the COG Rare Tumor committee collaborated with the Alliance for Clinical Trials in Oncology in a randomized trial of FOLFOX (leucovorin calcium (folinic acid), fluorouracil, oxaliplatin) alone or combined with atezolizumab, a PD-L1 inhibitor, for patients with stage III colon cancer and deficient DNA mismatch repair or microsatellite instability (ATOMIC, A021502, NCT02912559). This partnership enabled expansion of enrollment to include children aged 12–17 years and exemplifies the benefits of cooperative science for populations with rare tumors.

1.4. Adrenocortical tumors (ACTs)

ACTs occur at a rate of approximately 0.2–0.3 cases per million children per year in the US; [8,9] 50% are associated with a germline *TP53* alteration [10,11]. The recently concluded COG ARAR0332 trial corroborated work previously reported by the International Pediatric Adrenocortical Tumor Registry demonstrating favorable outcomes for patients with stage I observed post-surgery and a dismal prognosis for patients with stage IV disease [12–14]. Patients with stage III who underwent resection of the primary tumor, retroperitoneal lymph node dissection (RPLND), and treatment with mitotane plus chemotherapy

achieved outcomes comparable to stage I patients (95% 5-year overall survival) but patients with stage II disease (tumors $\geq$ 100 g or 200 cm^3) who underwent resection of the primary tumor and RPLND had poor outcomes, potentially due to variability in the use and extent of RPLND, omission of chemotherapy, biologic factors, or interference with immune surveillance. There is ongoing work studying methylation patterns and immunophenotype to differentially risk stratify these tumors. COG is currently collaborating with the Alliance for Clinical Trials in Oncology consortium, part of the NCI-funded National Clinical Trials Network, to develop a clinical trial for patients > 12 years of age intended to study tyrosine kinase inhibition (TKI) plus checkpoint inhibition versus TKI monotherapy [15,16].

1.5. Retinoblastoma

Retinoblastoma is the most common eye tumor of childhood, yet only 300 children are diagnosed annually in the US [17]. Past COG trials contributed 1) to a better understanding of high-risk histopathologic factors after enucleation in patients with unilateral disease (ARET0332) and 2) to improved outcomes in patients with non-CNS extraocular disease (ARET0321) treated with multimodal therapy [18,19]. Despite excellent survival for patients with intraocular retinoblastoma, relapse remains a common phenomenon, and patient survival does not equate to ocular survival. Thus, the current focus is on elucidating the relative contributions of individual interventions to ocular salvage. Another important outcome measure that has not been adequately addressed are long-term visual outcomes. The ongoing clinical trial, ARET2121, will explore the feasibility of incorporating intravitreal melphalan injections with neoadjuvant systemic chemotherapy in patients with newly diagnosed group D retinoblastoma with vitreous seeding.

In addition, advances in liquid biopsy applications have facilitated the detection of ctDNA in the blood and aqueous humor [19]. Prospective studies are evaluating the impact of specific chromosomal alterations and tumor fraction on prognosis for eye salvage and monitoring for recurrence.

1.6. Thyroid cancer

Differentiated thyroid carcinomas (DTC) are rare in young children but represent almost 10% of all malignancies diagnosed in older adolescents and are a common site of subsequent neoplasm in childhood cancer survivors [20,21]. Papillary thyroid cancer (PTC) comprises greater than 90% of pediatric DTC, is more likely to be characterized by oncogenic fusions than PTC in adults, and is clinically more likely to present with regional lymph node involvement, extra-thyroidal extension, and pulmonary metastases. Despite this, outcomes are excellent with disease-specific mortality under 2%. For most patients, thyroidectomy accompanied by compartment-oriented dissection of involved lymphatic basins are the cornerstones of treatment with additional radioactive iodine therapy in patients at intermediate or high risk for recurrence [22]. The low disease-specific mortality coupled with an absence of the need for traditional chemotherapeutic agents to treat DTC has resulted in the majority of patients being treated by providers other than pediatric oncologists and has posed difficulties for studying DTC under the aegis of the COG. However, a small minority of patients present with extensive local-regional or distant metastatic disease in the setting of a targetable mutation (e.g., BRAF, TRK, RET fusions) and present an opportunity for future studies of adjuvant or neoadjuvant targeted treatment to improve patient outcomes [23]. Data on the genetic landscape of DTC is being collected through the Molecular Characterization Initiative (MCI) of the National Cancer Institute (NCI) in partnership with the COG and will be used to inform proposed future initiatives in high-risk PTC.

1.7. Melanoma

Melanoma accounts for less than 5% of all skin cancers in the US, but causes the overwhelming majority of skin cancer-related deaths [24]. In the pediatric and adolescent population, melanoma is the dominant skin cancer diagnosis, yet children account for only ~1–4% of all melanoma cases [25–27]. Melanomas in the pediatric population often present atypically, with clinical findings failing to meet conventional ABCDE detection criteria (Asymmetry, irregular Borders, Color variation, Diameter >6 mm, lesion Evolution), leading to diagnostic delays. An additional complicating factor in the management of melanoma in pediatric and adolescent patients are those melanocytic skin lesions identified with Spitz morphology, more commonly developing during the first two decades of life and ranging in clinical behavior from benign to malignant (i.e., benign Spitz nevus, atypical Spitz nevus, Spitz melanocytoma, Spitzoid melanoma) [28–30].

Controversies pervade the literature regarding histopathologic and molecular features necessary to confirm diagnosis of an atypical Spitz tumor, malignant potential of the lesion, long-term prognosis, and recommended clinical management. It remains a challenge to predict which patients will experience metastasis or death due to an atypical Spitz tumor; such challenges translate into widely variable surgical and systemic treatment approaches. Significant advances have been made in the care of melanoma in adults over the past decade, however pediatric-specific treatment and outcome data remains lacking. The COG Rare Tumor Committee has formed a Melanoma Taskforce to lead concept proposal development for pediatric and adolescent patients diagnosed with cutaneous atypical and malignant melanocytic tumors.

1.8. Tumor biology

Understanding the biology of these rare tumors is critical for developing future therapeutic strategies. However, rare cancers are underrepresented in tumor biorepositories, making their biology difficult to study and highlighting the need for more national and international collaborative efforts [31]. In COG, biology specimens from children with all types of cancers are collected under an umbrella biobanking protocol known as Project:EveryChild (APEC14B1, NCT02402244). Despite these efforts, children with rare tumors are underrepresented on Project: EveryChild. While this study has enrolled more than 42,500 children with cancer as of May 2023, only 1047 (2.5%) have one of the diagnoses currently defined under the rare tumor category listed above compared with the approximately 9% of pediatric cancer patients impacted by these tumors [31]. Treating institutions usually prioritize contributing specimens when patients are enrolled on therapeutic studies, but therapeutic trials are lacking for many rare cancers. To incentivize enrollment, COG with NCI support began offering higher per-case reimbursement for rare cancers and began offering clinical sequencing for these tumors through the Molecular Characterization Initiative in 2022 (see below). Together, these initiatives have begun to increase enrollment even in the absence of a therapeutic clinical trial.

1.9. Molecular Characterization Initiative (MCI)

The MCI is a joint endeavor between the National Institutes of Health Childhood Cancer Data Initiative (NIH CCDI) and COG offering comprehensive DNA sequencing and ribonucleic acid (RNA) fusion testing to children and adolescents and young adults with CNS tumors, soft tissue sarcomas and rare tumors eligible for Project:EveryChild (see Table 2). Somatic DNA and RNA analyses and cancer predisposition-related DNA germline sequencing results are returned to the treating team and patients/families in approximately 3 weeks, at no charge to patients, families or treating institutions. Additional whole exome sequencing and methylation data are collected for research purposes. The rare tumor MCI cohort was initiated in September 2022 and enrollment to Project:EveryChild has increased since activation. We

Table 2
List of eligibility criteria for MCI.

Rare Tumors Molecular Characterization Initiative Eligibility Criteria
• Known or suspected rare tumor as defined inTable 1
• New diagnosis (relapsed/refractory specimens are not eligible)
• Enrollment within 6 months of diagnosis
• Age $\leq$ 25 years old
• Ability to test both germline peripheral blood and pre-treated tumor tissue (primary or metastatic)

anticipate that the MCI will continue to serve as a resource for patients and families, and for laboratory and clinical studies in rare tumors.

1.10. Cancer predisposition

It is important to consider the potential for underlying cancer predisposition in any child diagnosed with a rare tumor. The recognition of germline cancer risk may influence treatment considerations and allow for early detection of subsequent malignant neoplasms. Some of the tumors included in the Rare Tumor Committee have longstanding and classic associations with cancer predisposition syndromes with consensus surveillance guidelines for early detection and management of associated tumors. These include adrenocortical carcinomas and Li-Fraumeni syndrome (*TP53*), pleuropulmonary blastoma and *DICER1* tumor predisposition (*DICER1*) and hereditary retinoblastoma (*RB1*) [32–34]. Identifying a cancer predisposing mutation impacts not only the child but other family members who may undergo subsequent testing and surveillance. As germline sequencing of children with rare tumors expands, the expectation is that other cancer risk genes will be identified (for example, *MSH2*), some of which may only have emerging evidence of association with pediatric tumors when they are heterozygous, but which have clear implications for a parent who may carry the mutation and for the patient as they mature.

2. Challenges of rare tumor research

Rare tumor research faces many challenges, particularly limited accrual, clinical heterogeneity, poor understanding of natural history and biology, lack of novel therapies and inadequate funding and infrastructural resources. These present significant medical, logistical, statistical and feasibility barriers in advancing the field in rare tumors.

2.1. Classification

Some neoplastic lesions (e.g., paragangliomas) may not be captured under the rare tumor umbrella if they are considered to have benign behavior when localized; however, many of these tumors have limited treatment options when the tumor becomes disseminated. We must develop strategies for inclusion of patients with pre-malignant/borderline tumor types to ensure that the unique biology of these tumors and biomarkers of outcome may be better understood, allowing for development of clear treatment guidelines for this often challenging cohort of tumors in which malignant potential is poorly defined.

2.2. Clinical heterogeneity

In rare tumors, we need to study not only the impact of systemic chemotherapy or chemo-immunotherapy but also the roles of radiation, surgery and other aspects including non-pharmacologic, genetic, epigenetic, and environmental influences and impact of health disparities. While these needs exist in many cancer types in children and adults, these are especially challenging when considered in the context of rare tumors with limited accrual.

As ongoing MCI efforts reveal the scale of heterogeneity across rare tumors, we anticipate added challenges for clinical research in these cohorts. One potential challenge is that subcategorization of rare tumors, through clinically and molecularly-defined risk stratification, may reduce the size of each individually-defined cohort and increase the need for larger catchment areas and collaboration. Conversely for some rare tumors, or in tumors seen in both pediatrics and adults, molecular characterization may reveal shared biology and/or overlap among tumors resulting in expanded therapeutic options for some pediatric patients, especially those with targetable molecular alterations [35].

2.3. Logistical constraints

Rare tumor trials are often limited by financial constraints. Despite specific incentives such as Childhood Cancer STAR Act and Reauthorization Act, pharmaceutical companies may be less motivated to fund rare tumor trials, recognizing a limited market post-approval. Philanthropic and foundational support continues to play a critical role in raising awareness as well as raising funds to support rare tumor research. COG and other rare cancer research initiatives must continue to collaborate with philanthropic, governmental and industry resources to develop novel therapies and pathways to fund rare tumor trials. Collection and analysis of necessary preclinical data is also limited by scarcity of preclinical models of many rare tumors. Additional challenges include those inherent to conducting studies within multi-institutional consortia. The rarity of the disease and the multidisciplinary approach necessary often discourage smaller institutions from participating in a study, and adherence to a specific clinical protocol for a heterogeneous disease can be difficult. However, there is increasing enthusiasm and understanding of the need for prospective multidisciplinary studies.

2.4. Statistical challenges

Both small trials with multiple subsets as well as larger basket trials will require novel statistical methods for analysis and approaches to feasibility that consider the underlying epidemiology. In rare tumors, it may be necessary to use a historical control cohort or a non-equal randomization study design. While historical controls have the potential for bias, their value is recognized by regulatory agencies, especially in pediatric oncology settings. Several COG phase II trials have been designed to compare outcomes under the experimental treatment to that from the historical controls. These historical controls could be evaluated using different approaches, such as outcomes from a single time point, a fitted survival curve, or patient-level data. Our experiences are that the potential weaknesses of these approaches may be mitigated by carefully reviewing patients' eligibility criteria and selecting subjects comparable to the treatment group. This requires a good understanding of the historical control data and other considerations such as improvement in the standard of care, changes in disease diagnosis and evaluation criteria. Careful review is needed to evaluate the pros and cons of various analytic approaches with respect to the realistic constraints imposed by available treatments, the patient population and other resources. In general, these constraints necessitate testing therapeutic strategies for which there is an expectation for significant effect size.

3. Strategies

3.1. International collaboration

Regardless of statistical or logistical approach, international collaboration is a key priority to advance care for children with rare tumors. International collaboration widens the catchment area for a particular trial; however, the goals of international collaboration are not limited to increased accrual. In rare tumors, collaboration is especially critical as competition between groups may further limit availability of biospecimens or slow patient accrual to a particular trial, potentially leading to early closure.

International collaboration may include sharing of clinical queries to

build a network of experts and data, retrospective analysis of existing data sets or biospecimens and collaborative design of prospective trials, with shared, parallel or strategically complementary designs. The latter may include collaborative trial design using two or more treatment regimens with harmonized data collection and endpoints ("pseudorandomized") so that outcomes may be strategically compared.

Utilization of shared resources such as Pediatric Cancer Data Commons (PCDC)/Data for the Common Good (D4CG) may facilitate retrospective analyses and harmonize data collection. As in the NPC trial above, harmonized data collection from the start will allow for larger analyses, and the ability to control for multiple variables. Collaboration with the PCDC is enabling analysis of retinoblastoma data from multiple institutional registries as well as completed cooperative group trials to answer critical questions that cannot be answered by individual institutions given the rarity of the disease. Substantial work is needed upfront to accomplish this as all data collection fields need to be harmonized; these are time intensive but likely high yield endeavors.

Rare tumor registries may also provide key data to inform future prospective COG and external collaborative group trials including natural history/clinical outcome data as well as laboratory and translational data that drive novel trial concepts. The International PPB/*DICER1* Registry has provided the historical comparator and preliminary data for the therapeutic strategy to be tested in the planned COG trial (ARAR2331). Similarly, investigators with International Pediatric Adrenocortical Tumors Registry are leveraging specimens and data from COG to validate methylation profiling as a prognostic biomarker for potential use in risk stratification for a future COG trial.

While there are substantial current logistical and legal challenges to the development of shared prospective trials, we recognize that addressing these barriers to enable international prospective trials may have broad impact on efficiency of future rare tumor trials.

3.2. Multidisciplinary involvement

Many children, adolescents and young adults with rare cancers are cared for collaboratively or in some cases exclusively by physicians who are not primarily pediatric oncologists (such as retinoblastoma – ocular oncologists; thyroid cancer – endocrinologists; melanoma – dermatologists and surgeons; colorectal carcinoma – medical oncologists and surgeons). As a rare tumor committee, we are actively seeking to engage member institution-based multidisciplinary collaborators across the disciplines that care for patients with rare tumors.

3.3. Inclusivity

At the consortia and institutional levels, we must consider equity and inclusion in our clinical trial design and patient accrual and address both participant factors as well as institutional and consortia factors (e.g., funding, staffing, logistical hurdles) which limit inclusion and ensure social determinants of health are considered in study design and analysis.

As more individuals and families choose to participate in research, we also must carefully consider how best to relay the results of rare cancer research to participants who make these advances possible and leverage opportunities to engage with rare tumor survivors to ensure ongoing patient/family education. Additionally, we recognize our patients and their families as stakeholders and invaluable contributors to our future research models.

Despite these challenges, we believe the COG Rare Tumor Committee is effectively poised to collaborate with external registries, patient advocacy groups and international consortia to synergize efforts to advance care for children and adolescents diagnosed with rare tumors. Collaboration, across disciplines, institutions and oceans remains a key priority.

Disclaimer

The views expressed in this presentation are those of the authors and do not reflect the official policy of the Department of Defense or the U.S. Government including the National Institutes of Health.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Samara Potter reports a relationship with Bayer Healthcare that includes: consulting or advisory.

Theodore Laetsch reports a relationship with Advanced Microbubbles that includes: consulting or advisory. Theodore Laetsch reports a relationship with AI Therapeutics that includes: consulting or advisory. Theodore Laetsch reports a relationship with Bayer that includes: consulting or advisory. Theodore Laetsch reports a relationship with GentiBio that includes: consulting or advisory. Theodore Laetsch reports a relationship with Jazz Pharmaceuticals Inc that includes: consulting or advisory. Theodore Laetsch reports a relationship with MassiveBio that includes:. Theodore Laetsch reports a relationship with Menarini that includes: consulting or advisory. Theodore Laetsch reports a relationship with Novartis that includes: consulting or advisory. Theodore Laetsch reports a relationship with Pyramid Biosciences that includes: consulting or advisory. Theodore Laetsch reports a relationship with Treeline Biosciences, Inc. that includes: consulting or advisory.

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