Children's Oncology Group's 2023 Blueprint For Research

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Abbreviations Key

Abbreviation	Term
COG	Children's Oncology Group
CCDI	Childhood Cancer Data Initiative
MCI	Molecular Characterization Initiative
FDA	Food and Drug Administration

Abbreviation	Term
RACE	Research to Accelerate Cures and Equity

Pediatric oncology in 2023 is a study in contrasts. Decades of multi-institutional clinical trials have led to dramatic increases in five-year survival rates across broad categories of childhood cancers. The number of survivors of childhood cancer continues to increase, estimated to be 500,000 in the United States as of 2020.[1] The genomic landscape of most pediatric malignancies has been defined through comprehensive sequencing projects, leading to refinements in risk stratification and identification of more specific targets for potential therapeutic intervention. Precision treatment, beyond traditional cytotoxic chemotherapy, radiation, and surgery, has become a reality for some pediatric cancers. Regulatory changes have provided significant incentives to pharmaceutical companies to include children in clinical trial research with innovative therapies.

However, each of these modern-day successes widens the gulf between challenges that remain. Improvements in outcome have not been uniform across all malignancies. The impressive gains seen in acute lymphoblastic leukemia and Hodgkin lymphoma stand in stark contrast to the absolute lack of progress in metastatic sarcomas and diffuse intrinsic pontine glioma. Although five-year survival is a convenient benchmark, its use obscures two important issues. First, five-year survival is not the same as ten- or twenty-year survival.[2] Too many five-year pediatric cancer survivors will still succumb to their primary malignancy. Second, early survival is not without cost. Standard treatments carry a substantial burden of acute and chronic severe and potentially fatal complications, including accelerated cardiovascular disease, endocrinopathies, stroke, and secondary malignancies.[3] The overall spectrum of late effects has not changed for most childhood cancer survivors because our most common treatment approaches have not changed substantially from those used in the 1970s. Despite its potential, precision treatment has not replaced cytotoxic chemotherapy and radiation for most pediatric cancers. Even more fundamental, clinical tumor sequencing to guide diagnosis and refine treatment is not broadly available to all children with cancer, especially at initial diagnosis. Finally, the economics of drug development drives much of the pharmaceutical industry's focus on targets relevant to the common carcinomas seen in adults rather than the less common alterations seen in leukemias and embryonal solid tumors seen in children.

In 2023, the Children's Oncology Group (COG) is poised to play a pivotal role to build upon the prior achievements in pediatric oncology and address the remaining challenges. Formed in 2000 by the merger of four legacy pediatric cancer cooperative groups, COG is the National Cancer Institute's clinical trials organization devoted to childhood, adolescent, and young adult cancers. Since 2000, COG has conducted over 330 clinical trials for common and rare pediatric malignancies. With a centralized biorepository, COG facilitates the collection, storage, and distribution of >100,000 biospecimens annually from clinical trial participants and non-study biobanking. With more than 220 member institutions in the United States, Canada, Australia, New Zealand, and Saudi Arabia, the vast majority of children with cancer in these countries are treated at a COG site. Given the relative rarity of pediatric cancer, multi-institutional collaboration is essential to the timely conduct of research and COG is uniquely positioned to do this in many pediatric and adolescent/young adult cancers.

To summarize COG's recent achievement and outline our plans for the future, COG's scientific committees are publishing their Blueprints in this special issue of *Pediatric Blood and Cancer* . Similar to the 2013 Blueprints, these summaries outline how COG will address the remaining challenges in pediatric oncology. Each Blueprint describes the priorities that the COG committees will pursue to improve outcomes for children with cancer by improving survival rates, reducing short- and long-term morbidity from treatment, improving our understanding of cancer biology, seeking to identify and reduce health disparities, and further identifying the causes of childhood cancer.

Although it was reported that 71% of children with cancer participated in front-line cooperative group trials in 1991-1994,[4]study enrollment fell to 26% in 2000-2003[5] and 20% in 2004-2015.[6] In a resource-constrained environment, it is not feasible to offer clinical trials for all cancer types. Instead, COG is focusing its trials on

malignancies for which the survival rate remains sub-optimal, including acute myelogenous leukemia, high-risk neuroblastoma, high-grade gliomas, and metastatic sarcomas. In addition, malignancies with a relatively high early survival rate but with a substantial burden of short-term and late effects (including Hodgkin lymphoma, medulloblastoma, localized sarcomas, and acute lymphoblastic leukemia) will be prioritized for clinical trials with the intent to reduce the negative impact of theraph without compromising high cure rates.

Since the majority of children with cancer do not now participate in front-line clinical trials, it is also essential to gather information and biospecimens from children who are not part of clinical trials. Project:EveryChild, COG's overarching registry and biobanking study, was launched in 2015 to capture valuable information and specimens from all children with cancer, not just those who enroll on clinical trials. Project:EveryChild replaced disease-specific biology studies to streamline data and specimen collection. It also includes optional consent for future contact, which has facilitated the conduct of multiple epidemiology studies through COG. As of 2022, over 44,000 children have enrolled on Project:EveryChild and more than 250,000 biospecimens have been collected. With the planned addition of neuroblastoma and renal tumors, Project:EveryChild will provide a unified mechanism for registration, data collection, biobanking, and consent for future contact for all pediatric cancers.

Project:EveryChild also provided an efficient platform to launch the Childhood Cancer Data Initiative (CCDI) Molecular Characterization Initiative (MCI) in March 2022.[7] To address the unequal access to molecular testing at diagnosis, MCI is open to children, adolescents, and young adults with newly diagnosed central nervous system tumors, soft tissue sarcomas, and selected rare tumors. Consent for MCI participation is obtained at the time of enrollment on Project:EveryChild, including collection of tumor and blood samples. Using COG's centralized biobank for tissue processing, MCI provides whole exome sequencing of tumor and blood, panel RNA sequencing of tumor, and tumor methylation classification (for central nervous system tumors only) in clinical reports returned to the treating institution within 14 days of receipt of material. MCI's comprehensive molecular reports may then be used to help refine a participant's diagnosis and may suggest specific treatment options. In addition, complete sequencing data are being transferred regularly to a publicly available storage site along with clinical annotation from COG. CCDI anticipates these data will be used for new discovery in the research community. Perhaps most importantly, MCI provides equitable access to comprehensive genomic sequencing of tumor and germline results regardless of where a child with cancer receives care across the COG network. As more molecularly targeted therapies become available, the value of comprehensive tumor sequencing will become even more apparent, and frankly necessary.

Historically, evaluation of novel agents in children was avoided or an afterthought, as evidenced by the median delay of 6.5 years between first testing of cancer drug in adults and the first testing in children, even when restricted to agents that were ultimate approved by the Food and Drug Administration (FDA).[8] Collaboration with the pharmaceutical industry is a key feature to COG's overarching strategy to improve outcomes. Over the past twenty years, data from COG studies have been used to obtain a pediatric labeling indication from the FDA for 15 agents in 19 diseases or molecular contexts (Table 1). Although four of these studies were conducted with regulatory intent, most were not designed with a plan for an FDA filing. Nonetheless, the reliability of COG institutions and data quality were sufficient to support regulatory approval. The full implementation of the Research to Accelerate Cures and Equity (RACE) for Children Act in 2020 sought to increase pediatric investigations by providing a regulatory requirement to include children in cancer clinical trials for agents that target a pathway of relevance in pediatric cancer.[9] In the post-RACE regulatory world, COG hopes to be viewed as the pediatric cancer clinical trial organization of choice by pharmaceutical partners.

To improve the outcomes for children with cancer, it is essential to ensure that success is experienced by all children with cancer regardless of social factors. Unfortunately, there are disparities in cancer outcome among children based upon race or ethnicity, socioeconomic factors, and proximity to a treatment center specializing in childhood cancer. Compared with incidence data from Surveillance, Epidemiology, and End Results Program, enrollment on front-line clinical trials[6] and COG's molecularly-matched treatment study (Pediatric MATCH)[10] mirror the racial and ethnic demography of the general pediatric oncology population,

suggesting relative equity of access to clinical trials within the COG network. However, COG studies have demonstrated disparities of outcome within individual treatment studies[11] and within a single disease group across multiple treatment studies.[12] We have also observed disparities in the lost-to-follow-up rate on our clinical trials.[13] Therefore, participation on a clinical trial is not sufficient to mitigate disparities in outcome or to maintain study retention. For these reasons, COG is committed to promoting diversity in study participation,[14]documenting outcome disparities when they occur, identifying the etiology of compromised social determinants of health, and developing interventions to eliminate disparities in access to treatment and in cancer outcomes.

The future challenges in pediatric oncology are daunting, but pediatric oncologists, pediatric oncology nurses, radiation oncologists, surgeons, pharmacists, and caregivers are inherently optimistic. Furthermore, the magnitude of a challenge can drive innovation. For example, the rarity of pediatric cancer necessitates multi-institutional and sometimes multi-natiohnal collaboration to a degree not experienced in any other field of medicine. The scope of the COG network allows us to test interventions on a near population scale, leading to broad adoption if successful. The strategies outlined in these COG Blueprints represent multi-disciplinaries plans to address our most vexing problems. Working together, we will improve the outcomes for children, adolescents, and young adults with cancer by restoring them to long-term health.

Table 1: Medications with Food and Drug Administration approved indication for children using data from COG clinical trial. Studies that received financial support from a pharmaceutical company are underlined. Studies that were fully funded by industry partners without support from the National Cancer Institute and developed with the intent for regulatory filing are in *italics* .

Year of pediatric labeling	**Agent**	**Indication**	**COG study**
2005	Nelarabine	T-cell leukemia/lymphoma	P9673
2006	PEG asparaginase	Acute lymphoblastic leukemia	1962
2011	*Erwinia asparaginase*	*Acute lymphoblastic leukemia*	*AALL07P2*
2011 2013	Imatinib	Ph+ chronic myelogenous leukemia Ph+ acute lymphoblastic leukemia	AAML0123 AALL0031
2015	Dinutuximab	Neuroblastoma	ANBL0032
2017	*Pembrolizumab*	*Hodgkin lymphoma, MSI-H, TMB-H*	*ADVL1621*
2018	*SC-PEG asparaginase*	*Acute lymphoblastic leukemia*	*AALL07P4*
2018	*Blinatumomab*	*Acute lymphoblastic leukemia*	*AALL1121*
2019	*Dasatinib*	*Ph+ acute lymphoblastic leukemia*	*AALL1122*
2020	Gemtuzumab ozogamicin	Acute myelogenous leukemia	AAML0531
2021	*Liposomal daunorubicin/cytarabine*	*Acute myelogenous leukemia*	*AAML1421*
2021	*Recombinant Erwinia asparaginase*	*Acute lymphoblastic leukemia*	*AALL1931*
2021	*Rituximab*	*CD20+ non-Hodgkin lymphoma*	*ANHL1131*

Year of pediatric labeling	Agent	Indication	COG study
2021 2022	*Crizotinib*	*Anaplastic large cell lymphoma, Inflammatory myofibroblastic tumor*	*ADVL0912*
2022	*Brentuximab*	*Hodgkin lymphoma*	*AHOD1331*

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