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Leveraging clinical trial populations and data from the Children's Oncology Group for cancer survivorship research

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Abstract

Children and adolescents diagnosed with cancer can now expect an average 85% five-year overall survival, with significant improvements in longer-term morbidity and mortality reported over the past several decades. However, the long-term impact of therapeutic agents and modalities introduced in recent years remains unclear and will require dedicated follow-up in the years ahead. The Children's Oncology Group (COG), a part of the National Cancer Institute's National Clinical Trials Network, with over 200 sites across North America and beyond, enrolls more than 10,000 patients onto research protocols annually, inclusive of front-line clinical trials and non-therapeutic studies. COG provides a platform to conduct survivorship research with several unique strengths: 1) a huge catchment to ascertain relatively rare but important adverse events, 2) study populations that are otherwise too rare to study in smaller consortia, including access to highly diverse patient populations, 3) long-term follow-up of clinical trial populations linked to the original trial data, and 4) a natural platform for intervention research. Enhancements in COG infrastructure facilitate survivorship research, including a COG patient registry (Project:EveryChild), availability of a

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long-term follow-up tracking resource, and successful deployment of various remote-based study procedures to reduce the burden on participants and participating institutions.

Introduction

Children and adolescents newly diagnosed with cancer are increasingly long-term survivors as five-year survival approaches 85% (1) and longer-term mortality beyond five years decreases (2). Nevertheless, risks for late morbidity and early mortality remain. While new treatment modalities, including systemic therapies, radiotherapy, and surgery, offer the promise of further reductions in acute and long-term morbidity, careful follow-up of current and future survivors of childhood and adolescent cancers is critical in order to determine if that promise will be realized (3). Many of the key historic and current pediatric oncology treatment strategies were developed through the Children's Oncology Group (COG) and its legacy consortia (4). As part of the US National Cancer Institute's (NCI) National Clinical Trials Network (NCTN) and Community Oncology Research Program, COG consists of >200 institutions concentrated in North America but also includes sites in Australasia and the Middle East. COG typically enrolls more than ten thousand patients onto study protocols each year. Historically, approximately 90% of children diagnosed with cancer <15 years of age in the US were seen at a COG site (5).

Within COG, its Outcomes and Survivorship Committee is charged with developing and overseeing research that captures key outcomes and improves survivorship (6,7). This includes a mixture of observational and intervention studies as well as the development and maintenance of long-term follow-up guidelines specific to survivors of childhood, adolescent, and young adult cancers (8,9). Given the large numbers of sites and patients treated with clinical trial and observational data available, the COG research infrastructure represents a unique platform to advance survivorship care. In this review, we provide an overview of current ongoing survivorship research within COG (Table 1) and highlight gaps that may benefit from future investment.

Genetic Epidemiology

Using the ALTE03N1 study (NCT00082745), COG established a mechanism to identify key adverse events in patients treated for childhood cancer, enabling us to better understand the molecular basis of these events. Currently targeted outcomes include cardiomyopathy, stroke, subsequent neoplasms, and avascular necrosis. In this groupwide study with approximately 100 participating sites, we have: 1) identified survivors of childhood and adolescent cancer who developed a validated key adverse event (cases); 2) identified survivors without an adverse event (controls) matched on key characteristics including follow-up time; 3) obtained therapeutic summaries and blood from cases and controls; 4) compared the frequency of genetic variants and gene expression in cases and controls, using constitutional DNA and RNA; and 5) explored the role and nature of gene-environment interaction in the development of these outcomes. Since 2004, 1,677 cases (199 cardiac; 70 stroke; 973 subsequent neoplasms; 254 avascular necrosis) and 2,330 controls have been enrolled as of September 2021. We have used this resource to describe the role of candidate single nucleotide polymorphisms (SNP; e.g., those associated with *CBR3*, *GSTM1*) (10,11),

curated SNP arrays (implicating *HAS3*) (12), and genome-wide association analyses (identifying *CELF4*) (13) in the development of cardiomyopathy. In addition, we have demonstrated that a risk prediction model using clinical and genetic factors performed better than one containing clinical factors alone in identifying patients at risk for subsequent brain tumors (14). While ALTE03N1 has been highly productive, it remains challenging for COG sites to ascertain these late adverse events, particularly once patients transition from primarily pediatric COG institutions to adult care and become lost to follow-up. Future linkages between COG data and national registries or administrative datasets like the National Childhood Cancer Registry may facilitate the ascertainment of some key adverse events like second cancers (15).

Studies of Proximal Biomarkers of Late Effects

Given the extended time interval between cancer treatments and subsequent late effects common in pediatric cancer survivors, COG studies have also focused on more proximal biomarkers. This includes research examining long-term reproductive and cardiovascular health. Treatment for cancer can compromise the future fertility of children, adolescents and young adults diagnosed with cancer (16). ALTE11C1 (NCT01793233) was designed to assess the impact of alkylating agents on anti-Mullerian hormone (AMH), a surrogate measure of ovarian reserve, among female lymphoma patients (17). The primary aims were to compare AMH between newly diagnosed lymphoma patients and community controls at baseline and at 12 months off therapy, and to describe the trajectory of AMH change. The study leveraged the COG infrastructure to open the study across over 90 institutions to enroll 206 participants, measuring AMH at five time points and collecting, in a prospective manner, exposure data and menstrual history. The study has set the stage for a randomized intervention study, ALTE2131, which will assess the utility of gonadotropin releasing hormone agonists in preserving ovarian reserve among patients receiving alkylating agents as part of upfront treatment regimens (18). While COG will be the lead network member, the NCTN provides the infrastructure to conduct the study among multiple cancer consortia thereby addressing fertility across the reproductive age spectrum for whom the issue of fertility is most pertinent.

Cardiotoxicity is another common serious late effect of cancer treatment, as anthracyclines and radiotherapy remain widely used to treat childhood cancers (19). Cardioprotectants such as dexrazoxane have been shown to lower the risk of anthracycline-related cardiac injury during or shortly after completion of cancer treatment in children (20). However, the long-term efficacy of dexrazoxane for preventing cardiomyopathy/heart failure (CHF) in childhood cancer survivors is not known. ALTE11C2 (NCT01790152) utilizes a cross-sectional study design to determine the long-term efficacy of dexrazoxane in long-term childhood survivors enrolled on legacy clinical trials that featured upfront dexrazoxane randomization. Retrospective analyses of survival outcomes using existing administrative datasets found no association between dexrazoxane use and increased mortality, second cancers, or relapse of the original cancer (21,22). The study also features prospective participation with an in-person echocardiographic assessment focusing on indices of left ventricular function (shortening and ejection fractions) and pathologic remodeling (wall thickness-dimension ratio), as well as blood biomarkers of cardiac injury and myocardial

stress (natriuretic peptides) (23). The prospective study recently met its accrual goal with 201 participants (median age of 29 years and 18 years since cancer diagnosis) enrolled across 73 COG sites. Given the challenges of locating and recruiting adult-aged participants, the prospective participation rate was 40% (<1% active refusal; remainder are considered lost or possibly passive refusals). However, an initial analysis of cardiometabolic traits among participants from institutions with >50% versus <50% participation rates showed no significant differences between the two groups (24). Analyses of the primary cardiac endpoints are ongoing, and when completed, should provide more definitive information on dexrazoxane as a cardioprotectant for childhood cancer patients.

Nevertheless, most children treated with anthracyclines do not receive dexrazoxane, and dexrazoxane, even if beneficial, is unlikely to confer full cardioprotection (20). Therefore, effective secondary prevention strategies are also needed. ALTE1621 (NCT02717507) is a randomized placebo-controlled trial to determine the efficacy of a low-dose beta-blocker (carvedilol) for CHF risk reduction in survivors with preserved systolic function but who received high-dose anthracycline exposure (25). The trial is informed by previous studies demonstrating efficacy in pediatric and adult non-oncology CHF populations yet remains unstudied in the pediatric oncology population. It is hypothesized that treatment of anthracycline-exposed survivors with low-dose carvedilol over two years will reduce chronic cardiac injury via interruption of neurohormonal systems responsible for chronic cardiac remodeling, thus decreasing the risk of HF. Similar to ALTE11C2, ALTE1621's primary end points include echocardiographic biomarkers associated with pathologic left ventricular remodeling and systolic function, and blood biomarkers of myocardial injury and stress. The study recently met its accrual goal with 196 long-term survivors. Analyses of cardiac endpoints will begin after the last participant completes follow-up in 2022. Ultimately, ALTE1621 may provide important information regarding a physiologically plausible pharmacological risk-reduction strategy for childhood cancer survivors at high risk for developing anthracycline-related CHF.

Overall, these three studies show that COG sites can prospectively perform comprehensive assessments for survivorship studies that focus on surrogate markers for important late outcomes. ALTE11C1 and ALTE1621 showed that studies that require multiple timepoints can be successfully completed. ALTE1621 further demonstrated that COG can conduct a randomized, placebo-controlled, double-blinded cardio-oncology trial (26). ALTE11C2 showed that young adult participants, many of whom are no longer actively followed by their original treating institutions can still be found and recruited for research. Nevertheless, loss to follow-up and potential response bias remain a concern, as 40% of patients were recruited from sites that had <50% participation rate.

Engagement and recruitment of new cohorts

High-risk neuroblastoma, once considered untreatable, now has a three-year event-free survival rate exceeding 50%, due to increasingly intensive multi-modal treatments that include high-dose chemotherapy, tandem stem cell transplantation, radiotherapy, and novel biologic agents including retinoids, immunocytokines, and immunotherapy that have been developed in the past two decades (27–29). However, given the rarity of these patients

at individual institutions, only a large multi-institutional effort can successfully recruit sufficient numbers of these high-risk survivors to better understand their burden of late effects. The LEAHRN Study (ALTE15N2) is focused on studying high-risk neuroblastoma survivors treated with contemporary therapy to estimate the prevalence of and risk factors for organ and neurobehavioral dysfunction and subsequent malignant neoplasms, and determine their impact on health-related quality of life. The study was designed as a cross-sectional, single evaluation of survivors, with potential for re-enrollment into a future prospective cohort. After four years, and across 90 participating sites, the study recently met its target accrual with 377 survivors (45% participation rate), representing the largest sample of high-risk neuroblastoma survivors treated between 2000–2016. The study will conduct a formal analysis to examine the representativeness of the enrolled cohort in the near future, but an initial review of the distribution of demographic and treatment risk factors among the LEAHRN cohort appears to be as expected for 5-year survivors of high-risk neuroblastoma. The relative accrual success can be attributed to the younger age of the survivors (many still followed in a pediatric center), the relatively short median time from diagnosis to enrollment (9.1 years, range 5–18 years), the engagement of both survivorship and neuroblastoma researchers, and a centralized project manager who supported sites with activation, enrollment and data collection. In addition to clinical and laboratory assessments and abstraction of treatment exposures, participants provided a blood sample and patients and parents completed psychological assessments. DNA will also be sequenced to examine genetic risk factors for select late effects. The LEAHRN Study provides a model for other efforts within COG to build cohorts of other understudied survivor populations, such as survivors with Down Syndrome, or rare cancers not represented in the large NCI-supported Childhood Cancer Survivor Study (CCSS) cohort such as germ cell tumor (further discussed below).

Remote based studies/interventions

Given the wide geographic distribution of COG sites and cancer survivors, COG studies have also begun to leverage remote centralized data collection and intervention dissemination. For example, the ALTE16C1 protocol (NCT03206450) developed remote procedures to assess testicular function among long-term osteosarcoma survivors treated with cisplatin and ifosfamide. These two agents form the backbone of contemporary osteosarcoma treatment as well as many other childhood cancers, but whose effects on testicular function remain incompletely understood, including potential impact on spermatic DNA and offspring (30,31). To address these knowledge gaps, ALTE16C1 is recruiting participants remotely in a cross-sectional study, with participating survivors being asked to complete questionnaires and to provide blood (for testosterone and other sex hormones), saliva (for DNA), and semen (for morphology and spermatic DNA to examine epigenetic changes), all through a mailed approach. The remote approach was developed to reduce barriers for these male young adult participants who largely are no longer actively followed by their original pediatric centers. As of September 2021, the study has enrolled 195 male survivors (toward an accrual goal of 265), with the concurrent enrollment of age-matched community controls. Remote approaches have helped buffer study accrual against COVID-related limitations at many cancer centers, as nearly 50% of accrued patients have been enrolled since February 2020.

The COG is also sponsoring two randomized clinical trials testing easily disseminated remote-based physical activity interventions. Most survivors of childhood and adolescent cancers live sedentary lifestyles (32). Therefore, increasing physical activity offers the potential to reduce treatment-associated late effects such as cardiomyopathy, obesity, insulin resistance, and dyslipidemia (33). ALTE1631, a randomized two-arm web-based physical activity intervention among children and adolescents with cancer (NCT03223753), is designed to evaluate the effects of a 6-month long rewards-based physical activity intervention on fitness, cardiometabolic health, inflammation, adipokine status, quality of life and school attendance. Both the intervention and control groups receive educational materials encouraging physical activity, including relevant modifications for common neuro-musculoskeletal deficits, a monitor to record activity levels, and access to a web-based platform to motivate increased levels of physical activity. Individual physical activity levels are uploaded from the activity monitor to the website and are converted to credits for small gift cards or prizes. Only the intervention group receives details about how to earn rewards, receives gift cards in real time, and has access to the portion of the website where they can interact with other participants. The control group receives gift cards after study completion and can only see their own activity levels on the website. Outcome evaluations are completed at baseline, the end of the intervention, and 6 and 12 months later. As of September 2021, the study is open at 107 COG sites, has enrolled 177 participants (toward an accrual goal of 384), and has an 86% participant completion rate.

The StepByStep Study (ALTE2031; NCT04089358) is a randomized controlled trial that tests the efficacy of a 6-month intensive multi-level intervention combining a Fitbit® wearable physical activity tracker, a private Instagram® group, and individualized goal setting followed by a 6-month maintenance phase to improve physical activity for participants currently age 15–20 years who are 3–36 months off therapy and not meeting physical activity guidelines. As of September 2021, the study is open at 77 COG sites and has enrolled 75 patients (65% White non-Hispanic, 25% Hispanic, and 20% non-White non-Hispanic) out of a total accrual goal of 384. The distance-based intervention avoids the requirement of specialized site training or resources. With the COVID-19 pandemic, observations (i.e., finger sticks with dried blood cards, height/weight, two-minute step test, research accelerometer) were adjusted to allow completion at home by participants with phone/video support by coordinating center staff. This home-based approach is a promising strategy for future survivorship studies to increase access for racially and ethnically diverse patients while also reducing burden to participants and COG sites (34–37).

Other COG Survivorship Resources

As part of a commitment to establishing registries that can be leveraged for studies of childhood cancer etiology and outcomes, COG launched the Childhood Cancer Research Network (CCRN) in 2007. Informed consent was obtained to enter the names and demographic information of newly diagnosed COG patients, including the option for future recontact to participate in non-therapeutic and prevention studies. Between 2008 and 2017, 54,519 children treated at COG member institutions were enrolled on CCRN (Figure 1a). CCRN was replaced by Project:EveryChild (PEC) in 2017. PEC expands upon CCRN by collecting additional information upfront on potentially important exposures (e.g., *in vitro*

fertilization) or underlying diagnoses (e.g., genetic disorders), banks biological samples, and includes the collection of future outcomes data as part of upfront consent. As of May 2021, there were 27,992 newly diagnosed childhood cancer cases enrolled in PEC (Figure 1b).

Studies that have compared CCRN enrollment with what would be expected per NCI's Surveillance, Epidemiology, and End Results (SEER) Program have found that CCRN captures around 36% to 42% of the expected number of individuals diagnosed with cancer before 20 years of age (38,39). Similar efforts to define PEC's coverage are now being planned. The proportion of eligible patients enrolled in CCRN generally declined with increasing age and differences were observed for specific cancer types and racial and ethnic groups. However, CCRN did provide a robust resource for epidemiologic investigations of childhood cancer and it has been leveraged for etiologic studies of osteosarcoma, neuroblastoma, Wilms tumor, germ cell tumor, Ewing sarcoma, rhabdomyosarcoma, and Langerhans cell histiocytosis (40–43). While these studies have largely focused on genetic susceptibility to the respective childhood cancer, they have also included extensive questionnaires and the collection of medical records. Among the medical records needed are those related to cancer treatment information. Unless participants on CCRN and PEC are also enrolled onto frontline COG clinical trials, these registries lack information on participants' treatment exposures.

Overall, as CCRN and PEC have matured, there is a growing opportunity for these resources to be utilized for survivorship studies, particularly for cancers not included in other national efforts, such as the CCSS. COG investigators have started to lay the groundwork for expanding etiologic studies of germ cell tumor and hepatoblastoma to also evaluate late effects in survivors of these cancers. Additionally, COG investigators are leveraging CCRN and PEC to design new studies of late effects in unique populations of childhood cancer survivors (e.g., individuals with Down syndrome) who are otherwise rare at single institutions and in smaller multi-institutional consortia settings. PEC's consent includes broad permission to collect routine long-term outcomes data. While funding constraints within COG at present limit this mechanism to ascertaining long-term relapse, second cancer, and vital status, it potentially can be a mechanism to collect a much broader range of important health outcomes.

While CCRN and PEC have created a mechanism by which key demographic and cancer diagnosis information can be collected from newly diagnosed patients, successful survivorship research will also require a mechanism by which to reach and trace those patients years later. Long-term follow-up of children poses challenges including special protections for minors, changes in name and family structure over time, and the lifestyle changes and mobility that come with young adulthood. Therefore, most COG member institutions are unable to continue active follow-up of their patients long after completion of their protocol therapy, often due to lack of resources needed to do so effectively and efficiently.

COG's Long-term Follow-up Center (LTFC; ALTE05N1; NCT00736749) offers COG institutions a centralized mechanism for collecting long-term contact information to retain patients after they complete COG protocols. Specifically, the goals of the LTFC are to: 1)

maintain regular, lifetime contact with patients to ensure currency of contact information and self- or parent-reported health status; 2) locate patients who are lost to follow-up; 3) provide updates of patient contact and follow-up to the COG Statistics and Data Center and to the patient's original COG institution. This is a critical component of the infrastructure for COG childhood cancer outcomes studies – especially those studies where investigators wish to contact the patients several years after patients have completed participation on a frontline therapeutic study. For example, the LTFC has been used to facilitate the identification and contact of otherwise lost participants for ALTE11C2 and ALTE16C1. Overall, 2,531 out of 3,504 (72%) of participants registered with ALTE05N1 have updated their contact information or completed a follow-up survey at least once, with a median follow-up of 5 years (range 1–15). As part of the NCI's Childhood Cancer Data Initiative, additional investment will bolster the future ability of the LTFC to maintain contact with patients (44).

Engagement of Understudied/Underserved Populations

Ensuring the participation of traditionally underserved populations in survivorship research is of paramount importance and has historically been a challenge. In the 2020 US Census, the population growth in racial and ethnic minority populations in the US (now approximately 40% of the overall population and >45% of children) emphasizes the critical need to ensure that minority populations are appropriately represented in survivorship research (45,46). COG clinical trial data have shown that racial and ethnic minority status, poverty, and public insurance are associated with higher relapse and death rates, and thus among survivors, a higher burden of late effects (47–49).

The CCSS, the largest longitudinal cohort of childhood cancer survivors diagnosed between 1970–1999, is less representative of the current general US population with only 18% of the cohort reported as a racial or ethnic minority (45,50). CCSS has nonetheless demonstrated important racial/ethnic disparities in late effects and survivorship care among minority and uninsured survivors (51,52). COG offers a potential platform to further study these disparities, with annual enrollment ranging from approximately 10,000 to 14,000 patients (Figure 2). Overall, >40% of COG enrolled patients are reported as belonging to a racial or ethnic minority group. Despite this opportunity, challenges exist. Annual enrollment varies with the availability of front-line therapeutic trials, and in 2020, the COVID-19 pandemic reduced access to non-therapeutic trials at many institutions. There also are mixed data about whether there is representative enrollment of racial and ethnic minorities on upfront therapeutic COG clinical trials (53,54). COG also does not currently have data on the rates of loss to follow-up by race and ethnicity, nor are there data on whether minorities are less likely to be offered or agree to participate in survivorship studies. To address these barriers, efforts are underway to improve the systematic collection of demographic and socioeconomic characteristics including self-reported race and ethnicity, income, education, and insurance. Supporting participation of traditionally underrepresented populations through the employment of known and innovative strategies is essential to reduce historical differential participation (55,56). Ensuring that consents, interviewers, and surveys are available in the primary language of participants will also improve participation among non-English speakers. An approach modeled after a recent culturally

sensitive intervention to improve engagement with survivorship care could also translate into improving participation in survivorship research (57).

Procedural, Funding, and Study Implementation Considerations

Development of a survivorship study within COG requires multiple layers of review and approval (Figure 3), first by COG's Outcomes and Survivorship Committee followed by COG's Scientific Council. Approved "concepts" can then be submitted to extramural funders for consideration. Funded applications then require review and approval by NCI's Division of Cancer Prevention and the National Institute of Health's pediatric Central Institutional Review Board before they can be activated throughout COG. The time interval from initiation of a study concept to full protocol activation within COG usually takes at least one to two years, and often longer due to the need to successfully obtain extramural funding. As noted in Table 1, most hypothesis driven (i.e., non-registry) COG survivorship studies are funded by relatively large NIH R01 grants or similar mechanisms. These extramural funds supplement COG's NCORP base which provides institutions with federal per case reimbursement, by covering additional research assessments (e.g., study echocardiograms, laboratory assessments, functional tests like the 6-minute walk) or other costs (e.g., drug or behavioral intervention delivery). Extramural funding is also needed to support data coordination and research staff at a study chair's institution, as survivorship studies are typically not coordinated by COG's central statistics and data center, which largely focuses on oncology therapeutic trials. The Outcomes and Survivorship Committee will assist interested investigators in navigating the COG process, and overall, the committee has been successful in supporting an increasingly wide range of studies focused on childhood, adolescent, and young adult cancer survivors.

Conclusion

COG offers a unique platform for survivorship research with its geographic reach and diverse institutions and patients. In particular, studies that focus on recently treated pediatric and adolescent-aged patients may be easier to conduct versus those that require recruitment of adult-aged survivors. Nevertheless, with a dedicated tracking resource and the development of remote study procedures, COG investigators have successfully enrolled young adult cancer survivors. Additional national resources and initiatives now coming on-line that may further increase opportunities for survivorship research within COG include the National Childhood Cancer Registry and the Childhood Cancer Data Initiative. Finally, administrative linkage of outcomes data (e.g., National Death Index, insurance claims datasets) with legacy clinical trial data maintained by COG may be another opportunity by which important late outcomes can be described (22,58). Such linkages also offer the advantage of minimizing participation bias, and thus ascertain outcomes from groups more likely to be underrepresented in prospective studies.

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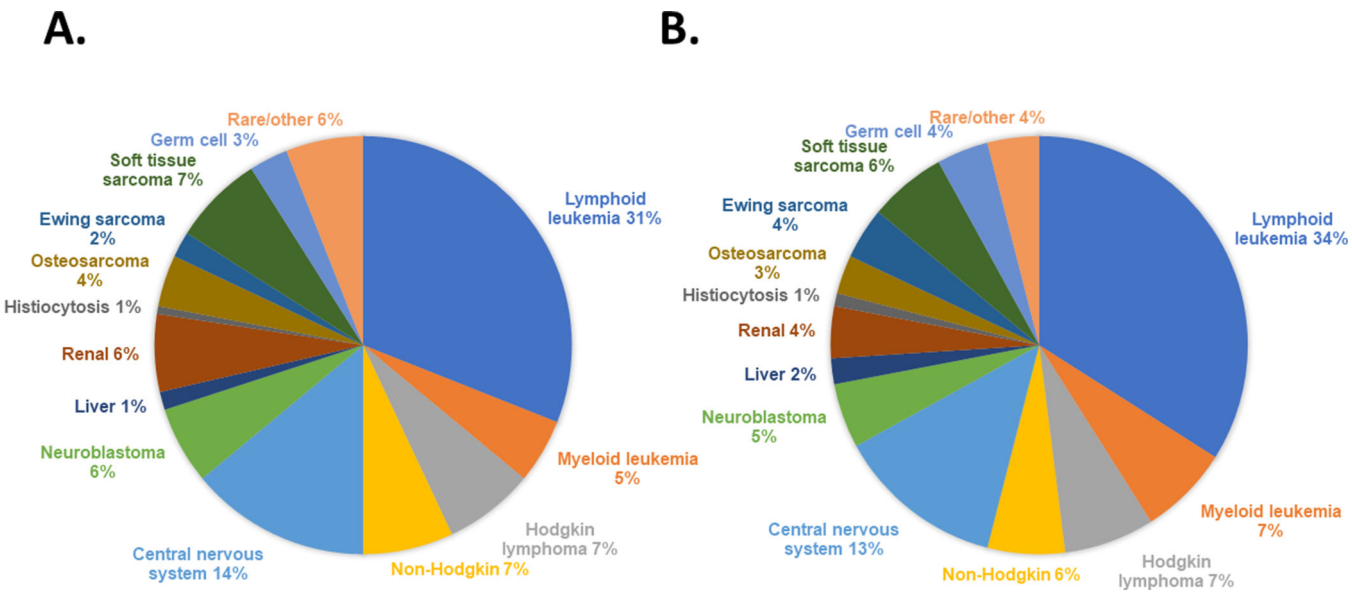

FIGURE 1.

Distribution of pediatric cancer cases enrolled in the Children's Oncology Group's (A) Childhood Cancer Registry Network from 2007 to 2017 (n=54,519), and (B) Project:EveryChild registry from 2017 through May 2021 (n=27,992).

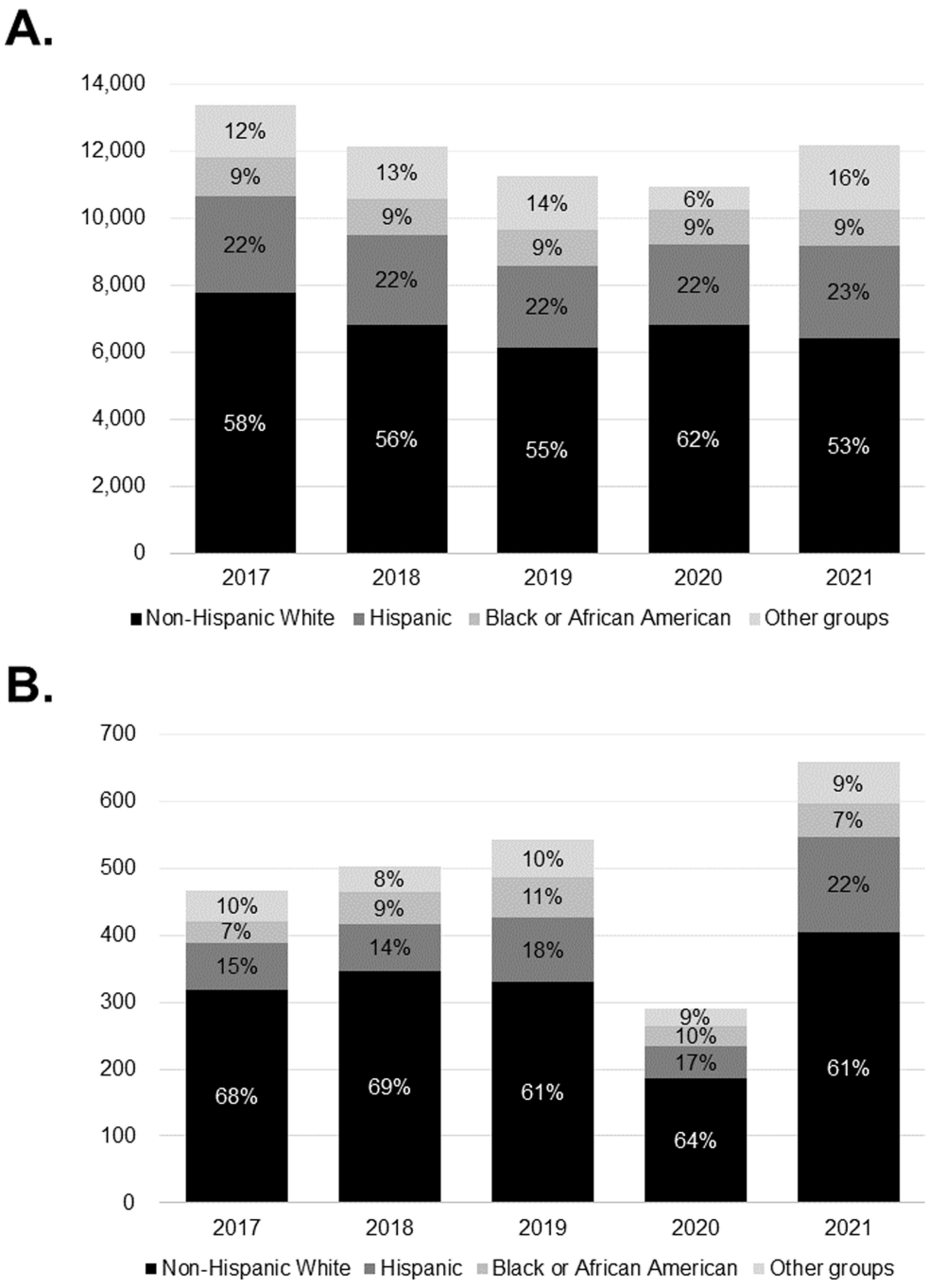

FIGURE 2.

Study enrollment within the Children's Oncology Group by race and ethnicity from 2017 to 2021, (A) overall, and (B) survivorship protocols specifically. Note that numbers may shift slightly over time as data are verified.

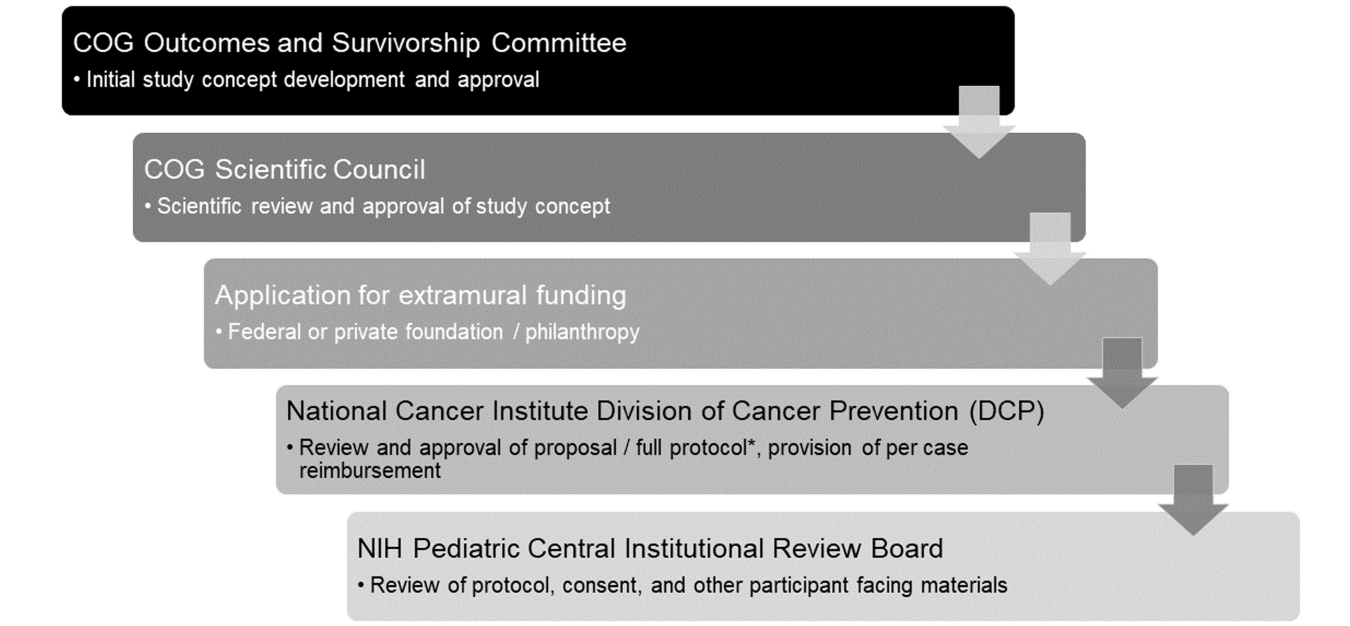

FIGURE 3.

Flow chart depicting the steps required to develop and implement a survivorship study within the Children's Oncology Group (COG), from concept to full protocol activation.

TABLE 1.

Current active survivorship protocols within the Children's Oncology Group (COG)

Protocol / study type	Primary goal	Funding*	Accrual / status†
ACCRN07 Childhood Cancer Research Network / registry	Registry of cancer patients seen at COG sites	NIH/NCI, private philanthropic funds	57,847 / closed, and now succeeded by APEC14B1
APEC14B1 Project:EveryChild / registry	Registry of cancer patients seen at COG sites with enhanced upfront collection of biologic specimens	NIH/NCI, private philanthropic funds	>30,000 / ongoing accrual
ALTE03N1 / observational case-control study	Genetic risk factors for key adverse late outcomes	NIH/NCI (R35CA220502)	~4000 / ongoing accrual
ALTE05N1 Long-term Follow-up Center / prospective cohort (infrastructure)	Long-term follow-up of COG patients	St. Baldrick's Foundation, NIH/NCI	Not applicable
ALTE11C1 / observational cohort	Longitudinal change in biomarkers of ovarian reserve during and following cancer treatment	Leukemia & Lymphoma Society	206 / met accrual goal, final data analysis
ALTE11C2 / cross-sectional study	Long-term efficacy of dexrazoxane as a potential cardioprotectant	Leukemia & Lymphoma Society, Rally Foundation, St. Baldrick's Foundation, NIH/NCI (R01CA211996)	201 / met accrual goal, final data analysis
ALTE15N2 LEAHRN / cross-sectional study	Health and psychosocial outcomes after high-risk neuroblastoma	St. Baldrick's Foundation	377 / met accrual goal, final data analysis
ALTE16C1 / cross-sectional study	Effect of cisplatin and ifosfamide on testicular function	NIH/NCI (R01CA175216)	195 / ongoing accrual
ALTE1621 PREVENT-CHF / randomized clinical trial	Efficacy of carvedilol in preventing left ventricular dysfunction	NIH/NCI (R01CA196854)	196 / met accrual goal, follow-up of remaining on-trial patients
ALTE1631 / randomized clinical trial	Promotion of physical activity in school-age survivors of childhood cancer	NIH/NCI (R01CA193478)	177 / ongoing accrual
ALTE2031 StepByStep / randomized clinical trial	Promotion of physical activity in adolescent and young adult cancer survivors	NIH/NCI (U01CA246665)	75 / ongoing accrual

NCI, National Cancer Institute; NIH, National Institutes of Health

*NIH grant number if available; for some studies, COG sites received additional supplemental per case reimbursement from NCI for each enrolled study participant.

†As of September 2021.