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Current and Coming Challenges in the Management of the Survivorship Population

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Abstract

With the widespread adoption of multi-modality treatment, 5-year survival of children diagnosed with cancer has improved dramatically in the past several decades from approximately 60% in 1970 to greater than 85% currently. As a result, there are an estimated nearly half a million long-term survivors of childhood cancer living in the United States today. However, survivors have, on average, significantly greater serious medical and psychosocial late effects compared with the general population. In this review, we will discuss the current epidemiology of childhood cancer

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Declaration of interests

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survivorship, including new methods to estimate the burden of late effects and genetic susceptibility towards late effects. We also will review the development of surveillance guidelines for childhood cancer survivors and early toxicity signals from novel agents now being tested and used increasingly to treat pediatric and adult cancers. We conclude with an overview of current models of survivorship care and areas for future research.

Introduction

Over the past 50 years, multi-institutional cooperative group clinical trials have led progressive advancements in risk-stratified, multimodality cancer therapy and hospital care for children with cancer, resulting in substantial improvement in long-term survival. Data from the United States Surveillance Epidemiology and End Results program demonstrated a 5-year survival of 61.5% among children diagnosed before 20 years of age from 1975–1977 compared with 85.7% among those diagnosed from 2009–2015 (Figure 1).¹ As a result, there are nearly 500,000 survivors of childhood cancer living in the United States today.² Unfortunately, cure is not without consequences, and long-term survivors, on average, experience significantly greater medical and psychosocial late effects compared with the general population. In this review we provide an overview of: 1) the epidemiology of childhood cancer survivorship, including new methods to estimate the burden of late effects; 2) the current knowledge regarding genetic susceptibility to late effects; 3) the development of surveillance guidelines; 4) novel agents and their potential impact on survivorship issues; and 5) models of survivorship care. We conclude with some proposed future directions for research in this field.

Epidemiology of Childhood Cancer Survivorship

Childhood cancer survivors are at risk for early mortality, secondary malignant neoplasms, and treatment-related organ damage. These impairments impact physical, cognitive and emotional health, and influence optimal participation in life roles at home, at school, at work, and in the community. The burden of chronic disease is high, with more than 50% of survivors experiencing at least one, severe, disabling, life-threatening, or fatal chronic health condition by age 50 years, a rate nearly five times greater than expected when compared with siblings (Table 1).³ Cognitive impairment is also prevalent at a higher than expected rate (22.8% among survivor versus 10% among siblings),⁴ and emotional distress is not uncommon (15% vs. 10% expected).⁵ These documented late effects can often be attributed to cancer and treatment related risk factors (Tables 2 and 3). As a result, survivors have been more likely to utilize special education services at school and less likely to graduate from college,⁶ more likely to be unemployed,⁷ and on average, have lower incomes,^{8–10} and more likely to receive public benefits to supplement their incomes than the general population (Table 4).^{11,12} Overall, moderate or severe financial hardship has been reported by half of all survivors.¹³ In addition, survivors are twice as likely as siblings to live dependently,¹⁴ and significant proportions (15–20%) report long-term poor physical, mental, or general health.¹⁵ However, for many groups of long-term survivors, those treated in more recent eras appear to be experiencing reduced late mortality¹⁶ and serious chronic conditions,¹⁷

although these gains have not been uniform, and have not necessarily corresponded with improved self-reported health status.¹⁸

However, until recently, traditional measures such as frequencies, incidence and prevalence were used to describe the burden of late effects associated with surviving childhood cancer. However, since these measures report simple counts or proportions with time to a first event, investigators have had to limit analyses of outcomes to single exposures, primary cancer subtypes or few late effects of interest. Although several studies have described long-term morbidities across entire survivorship cohorts, these efforts rarely describe recurrent events and multiple chronic conditions.^{3,19–21} In a population where substantive multimorbidity (two or more concurrently existing chronic health conditions) and excess early mortality are observed, a comprehensive perspective of disease burden in this population was lacking.^{16,22}

The mean cumulative count (MCC) and cumulative burden approaches both provide analytic options that allow investigators to account for multimorbidity by describing both the magnitude and diversity of chronic health conditions in a cohort of individuals (Table 5).^{23–25} Both measures account for competing risk and censoring and thus differ from incidence and prevalence or traditional count statistics. While the MCC accounts for each event regardless of type, the cumulative burden applies a structured clinical ruleset based on the pathophysiology and recurrent nature of each measured chronic health condition thus allowing for a more clinically appropriate perspective. Using the cumulative burden metric, a recent analysis from the St. Jude Lifetime Cohort Study found that by age 50, a survivor experienced, on average, nearly 5 chronic health events graded as severe/disabling, life-threatening or fatal, a number nearly twice that observed in matched community-controls.²⁵ Additionally, the analysis highlighted that the survivorship population is not a monolithic population but is quite heterogenous in its composition in relation to observed late effect patterns (Figure 2).

While prospective follow-up data from large cohort studies can yield important insights, simulation modeling can provide complementary insight on long-term health outcomes. By extrapolating data beyond the period of observation and reflecting age-related competing mortality risks, model-based estimates of life expectancy among 5-year survivors of childhood cancer project that on average, cumulative excess mortality risks associated with late effects may reduce survivor life expectancy by more than 10 years.²⁶ Comparable to estimates for the general population (or other disease populations), summary measures of population health, such as life expectancy or quality-adjusted life expectancy, can quantify the impact of treatment-related late mortality risks on length and quality of life, as well as serve as benchmarks for tracking improvements in survivor health over time. For example, survivors diagnosed in the 1990s are projected to live longer into adulthood than those diagnosed in the 1970s, suggesting evolving treatment approaches have led to improved life expectancy after treatment for childhood cancer.²⁷

Additionally, by synthesizing data from multiple sources, including randomized controlled trials, observational studies, meta-analyses and expert opinion, projecting long-term outcomes, decision modeling provides a valuable analytic framework for simulating the health outcomes associated with various follow-up care strategies for survivors.²⁸ Previous

studies have evaluated the Children's Oncology Group (COG) long-term follow-up recommendations to prevent congestive heart failure,^{29,30} and more recently, secondary breast cancer among female survivors with a history of chest radiation.³¹ Decision modeling is increasingly used by policy makers developing guidelines to provide important insight on the tradeoffs between clinical benefits and harms associated with screening.^{32,33} Given the sample size and follow-up time needed, randomized clinical trials testing different screening strategies in survivors are unlikely. In this context, simulation modeling may be particularly useful for informing screening guidelines for at-risk survivors. As genetic markers of susceptibility for late-effects emerge, decision modeling provides an analytic framework to evaluate how this information can be used to refine and inform screening guidelines for at-risk survivors.

Genetic Susceptibility of Late Effects

Despite the strong and unambiguous relationship between therapeutic exposure and late effects in cancer survivors, there is considerable interindividual variability in risk for any given dose, suggesting the role for genetic susceptibility in possibly influencing individual risk.^{34,35} Considerable efforts have been expended attempting to identify genetic variants associated with late effects, to determine if the genetic variants can shed light on the underlying disease mechanisms and to incorporate the genetic variants to identify those at highest risk for developing these outcomes. In this section, we highlight our current understanding of the genetic modifiers of exposure-related late effects, such as anthracycline-related cardiomyopathy, subsequent malignant neoplasms, reproductive health issues, and neuropsychological impairment.

Anthracycline-related cardiomyopathy (Table 6)

Overall, the largest amount of activity has focused on anthracycline-related cardiomyopathy. Significant associations have been reported between cardiac compromise and a nonsynonymous coding variant in *RARG*,³⁶ in the *SLC* family of drug transporter genes,^{37,38} and genetic variants in *CELF4*,³⁹ *HAS3*,⁴⁰ and *CBR3*.⁴¹ The underlying mechanism for treatment-related complications has also been largely explored in anthracycline-related cardiomyopathy, with a role for alternative splicing of *TNNT2*, enzymes responsible for cardiotoxic metabolites, reactive oxygen species and mitochondrial injury.³⁹

Subsequent Malignant Neoplasms (Table 7)

PRDMI has been implicated in the development of radiation-related malignancies (primarily breast cancer) in Hodgkin lymphoma survivors.⁴² Other studies have identified genetic variants in *FGFR2*,⁴³ and in *PROX1* and *TAGLN*,⁴⁴ to be associated with radiation-related breast cancer. A recent genome-wide association study identified *HTR2A* to be associated with subsequent basal cell carcinoma.⁴⁵ Pathogenic or likely pathogenic germline mutations in genes known to be associated with autosomal dominant cancer predisposition syndromes with moderate to high penetrance have also been identified in 5% or more childhood cancer survivors. These mutations were associated with an increased risk for breast cancer and sarcoma among irradiated survivors.⁴⁶

Reproductive Health (Table 8)

Women with a *BRSKI* gene variant had a significantly increased risk for low serum AMH, though the impact of this genotype on age at menopause was not as strong as the impact of abdominal radiation.⁴⁷ Using a genome-wide approach, a recent study revealed a risk profile inclusive of four single nucleotide polymorphisms (SNPs) in the regulatory region of neuropeptide receptor 2 (*NPY2R*) that conferred a 25-fold increase risk for premature menopause among survivors exposed to ovarian radiotherapy, with results that were replicated in an independent cohort.⁴⁸ SNPs in androgen receptor genes (*ERα* and *ERβ*) expressed in the testis have been associated with oligo- and azoospermia; survivors carrying an *ERα* gene variant were 4-fold more likely to be azoospermic, a risk that increased to 5-fold in survivors exposed to alkylating agents or testicular radiation.⁴⁹ However, these findings need to be replicated in an independent cohort.

Neuropsychological impairment

Genetic variants in the *MTHFR* gene, glutathione S transferase (*GST*), monoamine oxidase (*MAOA*), methionine synthase (*MS*, also known as *MTR*), and nitric oxide synthase (*NOS*) have been associated with attention deficit disorders, reduced attentiveness and response speed and reduced overall intellectual function in several candidate SNP studies.^{50–54}

Understanding the molecular underpinnings of treatment-related complications serves two purposes: 1) identifying patients at highest (and lowest) risk, such that treatment or follow-up can be tailored; 2) understanding the mechanism of the treatment-related late effects and using this information to inform therapeutic strategies. There is early evidence that genetic variants can be used to identify vulnerable subgroups, and that information from these variants may improve the ability to predict outcomes better than if one only uses clinical and demographic variables. For example, multiple genetic variants in *SLC8A3* and other genes allowed the creation of risk prediction models for anthracycline-related cardiomyopathy, such that 75% of the patients in the high-risk group were accurately predicted to develop cardiomyopathy, while 96% of those in the low risk group did not develop cardiomyopathy.⁵⁵ It has also been possible to identify survivors of childhood cancer at high or low risk for subsequent radiation-related brain tumors on the basis of genetic and clinical information, and the genetic plus clinical model was superior to the clinical model alone ($p=0.002$).⁵⁶ Finally, patients in the highest tertile of radiation-interaction polygenic risk scores had a 60% higher risk of radiation-related breast cancer when compared with those in the lowest tertile.⁵⁷ These findings notwithstanding, a large gap remains between the knowledge gained through research and readiness for clinical application in cancer survivors. The logical next steps would be to incorporate these findings in patients newly diagnosed with cancers as well as cancer survivors in order to personalize the management of those at highest risk.

Development of Surveillance Guidelines

The risk for late therapy-related complications in childhood cancer survivors is the basis for focused screening. These late complications primarily result from therapeutic exposures (e.g., surgery, radiation, chemotherapy) employed during cancer treatment (Tables 2 and 3), although premorbid conditions, genetic predispositions, and treatment events can be

guidelines, screening recommendations and rationale, and references), and for patients or caregivers (in lay language).⁷¹ A summary of the cancer treatment history (typically part of a Survivorship Care Plan)⁷² is required to generate these exposure-related guidelines. This summary, which is ideally prepared by the treating oncology center at the end of therapy or at entry into survivorship care, is a key document to which survivors should have ongoing access, in order to assure that they are receiving the recommended guideline-directed follow-up care based on the specific cancer treatment that they received.

Identifying Late Effects of Novel Therapies

Current guidelines, such as those from the COG and other groups has largely focused on conventional cancer therapeutics, since there are now several decades of long-term outcomes data for many patients treated with these modalities and reasonable evidence supporting their associations with various late effects. However, in recent years a better understanding of the biology of many pediatric cancers has led to the development of multiple new agents that offer the promise of more effective and less toxic treatment (Table 9). Specifically, cancer treatments are becoming more personalized with previous histologic diagnoses now being increasingly subclassified based on molecular characteristics, and with subtypes potentially treated with different agents or combinations of agents that target the cancer's unique molecular or genetic aberration.⁷³ For example, an initial success came with Philadelphia-positive acute lymphoblastic leukemia, where the tyrosine kinase inhibitor (TKI) imatinib plus chemotherapy transformed 3-year event-free survival from <50% to ~80%.⁷⁴ The addition of other molecularly-targeted agents to conventional chemotherapy is now routine in subsets of acute myeloid leukemia, lymphoma, and sarcoma patients where specific tumor mutations appear amenable to such inhibitors (e.g., FLT3-internal tandem duplications, anaplastic large cell kinase mutations, NTRK fusions, respectively).⁷⁵⁻⁷⁷ The addition of antibody-based therapies to conventional chemotherapy has also improved outcomes for many pediatric malignancies. For example, dinuxtimab, rituximab, brentixumab, and gemtuzumab are already considered standard of care for certain newly diagnosed or relapsed neuroblastomas, lymphomas and leukemias.⁷⁸⁻⁸¹ Ongoing trials are testing the efficacy of other promising antibodies such as blinatumomab and inotuzumab,^{82,83} and the optimal role of immune checkpoint inhibitors and genetically engineered chimeric antigen receptor (CAR) T cells.^{84,85} For local control, surgery and radiotherapy also have evolved, becoming less invasive, or featuring new techniques and particles (e.g., protons) that more precisely target the tumor and limit dose to normal tissues.⁸⁶

Nevertheless, "targeted" agents may have off-target effects.⁸⁶ For example, some endocrine and immunologic late effects are beginning to emerge among children treated with targeted agents. TKIs have been associated with growth deceleration and alterations in bone mineral and thyroid metabolism. This includes children treated with imatinib for chronic myeloid leukemia (CML) who have since developed varying degrees of growth restriction.⁸⁷ Although case series in children treated with imatinib have reported normal thyroid function, other TKIs may affect thyroid function. In adult studies, nilotinib, dasatinib, sunitinib, and sorafenib have been associated with de-novo hypothyroidism, variably preceded by hyperthyroidism,⁸⁸ leading to a general recommendation that children receiving TKIs should also have their thyroid function closely monitored. Immune checkpoint inhibitors have also

been associated with hypophysitis and anterior pituitary deficiencies in adults.⁸⁹ Finally, B cell depletion occurs with agents that target B cell antigens (e.g., rituximab, blinatumomab). Although B cell aplasia is usually short-term, there is a potential for long-term B cell aplasia in patients who have chimeric antigen receptor T cell persistence.⁸⁵ The health impact of prolonged B cell aplasia is unclear but thought to be minimal so long as affected patients receive ongoing immunoglobulin replacement to minimize infectious risks. However, long-term financial costs may be important as these treatments become more widespread. To date, there have not been any reports of lymphoproliferative disorders or secondary malignancies directly related to CAR T cell products. Finally, the late cardiovascular effects of new targeted agents remain largely unknown in childhood cancer survivors. However, rare but serious toxicities including ischemic events (e.g., ponatinib) and autoimmune myocarditis (e.g., immune checkpoint inhibitors) have been observed in adults, including young adults.^{90,91}

Changes in clinical trial design and protocol development may affect the ability to comprehensively study the potential late effects of these novel agents. For example, the established paradigm of requiring large phase 2 or 3 trials to establish efficacy prior to an agent becoming standard of care may no longer apply in certain situations.⁹² Given the relative rarity of pediatric cancer, the subclassification of tumors based on genetic or molecular features further increases the heterogeneity of treatment while reducing the numbers of survivors treated similarly, potentially increasing the difficulty of detecting rare but serious late effects in the future. Therefore, long-term comprehensive follow-up of children treated with novel emerging therapies is critical to determining whether these therapies are truly associated with long-term improved outcomes versus historical treatments.

Models of Survivorship Care

One of the key recommendations made by United States National Academy of Medicine (formerly, the Institute of Medicine) regarding the care of cancer survivors was that there is a need for defining standards for *systems of comprehensive, multidisciplinary follow-up care that link specialty and primary care providers*.^{93,94} During their childhood and adolescent years, most childhood cancer survivors are transitioned from the acute oncology clinic to a specialized survivor clinic. In a survey of COG institutions, 84% of the 97 responding institutions indicated that they have a clinical program comprised of providers that specifically care for childhood cancer survivors.⁹⁵ Unfortunately, once these survivors are ready to transition out of the pediatric setting, specialized resources are less accessible. Only 38 of the 97 institutions reported access to specialized survivorship care in an adult care setting. Thus, most adult survivors of childhood cancer likely do not receive care in a survivor clinic or receive follow-up from a health care provider with expertise in survivorship issues.⁹⁶ Most receive their health care from a primary care physician, many of whom profess discomfort with caring for such survivors independently, have limited knowledge about survivor-specific follow-up guidelines,^{97,98} and are unlikely to provide recommended surveillance.⁹⁶

To address this gap, several models have been proposed for the care of adult survivors of childhood cancer, most of which are based on the concept of “shared care” between the cancer center and the primary care provider, with the balance of this care contingent on individual survivors’ existing late effects and risk for future morbidity.⁹⁹ Successful models of shared survivor care are context specific. For example, the Adult Long-Term Follow-Up Program at Memorial Sloan Kettering Cancer Center is located in an academic medical center and staffed by primary care physicians and nurse practitioners.¹⁰⁰ The clinic cares for higher risk survivors, particularly those with multiple morbidities, while lower risk survivors are transitioned back to community-based primary care. In Canada, the Pediatric Oncology Group of Ontario has launched an initiative to recruit family practice teams and academic family practice programs in community hospitals who are willing to care for adult survivors of childhood cancer who have been discharged from cancer-center based survivor care. The goal is to identify geographically diverse primary care practices (particularly those that have multi-disciplinary health care teams that include providers such as psychologists, social workers, dietitians, etc.) that are willing to take on a “critical mass” of survivors with the hope that this will incentivize their developing an expertise in survivorship. These clinics would then be provided with education from the province’s specialized cancer center-based survivor programs, which will remain accessible should specific patient advice be needed or if survivors need referral back into the cancer system.

As more survivors age in older adulthood, and as the size of the population of childhood cancer survivors continues to grow, it is clear that specialized survivor clinics will not have the capacity to care for all survivors. Several recently completed and ongoing clinical trials have evaluated novel approaches for ensuring that survivors receive recommended surveillance during adulthood. The *Evaluation of Cardiovascular Health Outcomes Among Survivors* (ECHO) trial demonstrated that telephone counseling from an advanced-practice nurse increased the rate of completion of echocardiography in survivors at risk for cardiac dysfunction when added to the provision of a printed survivor care plan.¹⁰¹ A similar benefit to providing a tailored telephone-delivered motivational interview was observed in a study focused on increasing the uptake of screening mammography in survivors at risk for secondary breast cancer.¹⁰² Unfortunately, such interventions are resource intensive and there is concern about whether and how these can be scaled to a growing population of survivors. Consequently, new research is investigating the use of mobile health technologies such as smartphone apps to deliver such counseling remotely. For example, a follow-up to the breast cancer screening study above is recruiting patients and their primary care providers to a study that uses a smartphone app that provides interactive 2-way text messages with links to video vignettes to activate survivors and their clinicians (NCT03435380). Further, the emerging capabilities of m-Health technologies that can facilitate communication between survivors and health care providers may overcome some of the geographic and time barriers to the receipt of appropriate survivorship care. Patient-reported outcomes such as pain and anxiety, biometric data such as pulse rate and blood pressure, and elements of the physical examination such as assessment of skin lesions by teledermoscopy,¹⁰³ can all be accomplished remotely. Similarly, the use of telemedicine, especially for patients who live in rural areas, has the potential to increase access to risk-based survivor care.¹⁰⁴

Future Directions

Decades of follow-up have been required to demonstrate improvements in long-term pediatric cancer outcomes to date.^{17,105} To facilitate this going forward in this era of increasingly personalized cancer medicine, a joint effort by the pharmaceutical industry, government, and non-governmental professional societies to organize infrastructure that enables such long-term follow-up is recommended. Such infrastructure should include, at minimum, the creation of a registry that allows for later linkage and ability to re-contact patients or families for follow-up information, or if possible, a more resource-intensive prospective cohort. Such efforts, in combination with information about individual genetic susceptibility to selected late effects, cost-effectiveness and decision modeling research, will enable the continued refinement of long-term follow-up guidelines. As these guideline refinements are realized, the clinician's ability to personalize screening and follow-up care for childhood cancer survivors will continue to improve, maximizing screening yield and timely intervention for those at highest risk, while minimizing the need for screening in survivors at low risk for late complications. However, these refinements can only be realized with effective dissemination, including among primary care providers.

Involvement of primary care and medical subspecialists is particularly relevant as survivors age. Premature aging and frailty are increasingly documented findings among survivors of childhood cancer.¹⁰⁶ As in older adults, frailty in childhood cancer survivors is associated with additional accumulation of chronic disease and with mortality. Thus, understanding when and how frailty develops among childhood cancer survivors, and identifying the pathology responsible for frailty onset, may provide biological targets for development of remediation and early intervention strategies.¹⁰⁷ Telehealth and other strategies to disseminate information to survivors and primary care providers will also be critical to develop and test. Overall, survivorship as a field has largely developed as a result of the tremendous progress in curing many cancers, the focus now needs to be directed at preventing or mitigating the long-term consequences of otherwise very successful cancer therapy.

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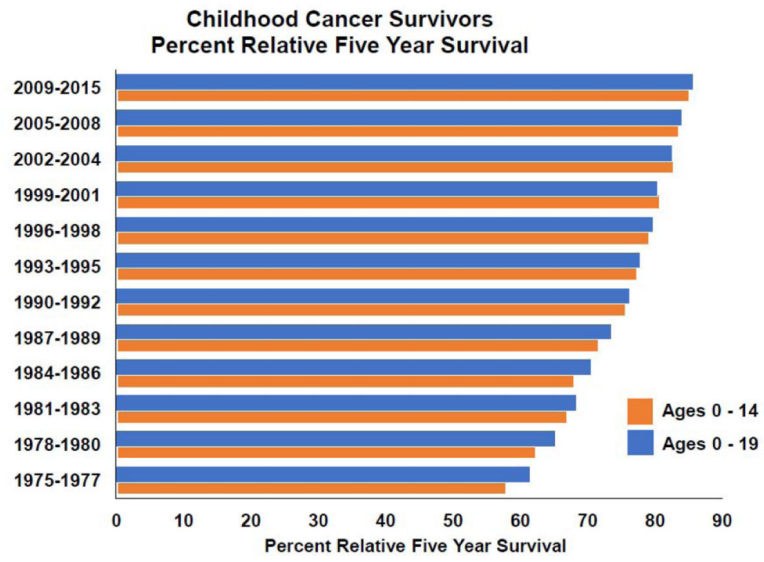


FIGURE 1. Childhood cancer survivors percent relative five year survival.

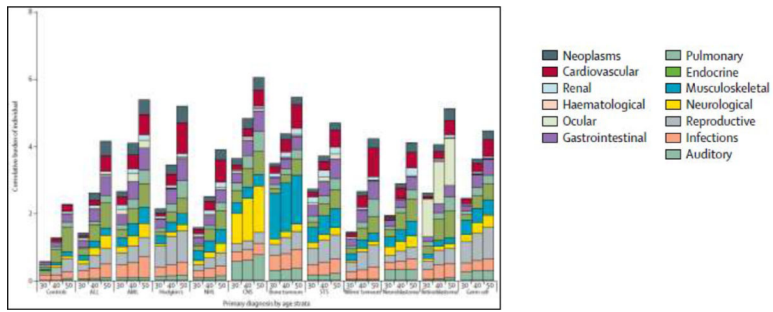


FIGURE 2. Distribution of cumulative burden of grades 3 to 5 chronic health conditions in the St. Jude Lifetime Cohort Study of childhood cancer survivors and community controls. X-axis shows age in years. Abbreviations: ALL, acute lymphoblastic leukemia; AML acute myeloid leukemia; CNS, central nervous system tumors; NHL, non-Hodgkin lymphoma; STS, soft tissue sarcomas. From Bhakta et al., Lancet 2017.

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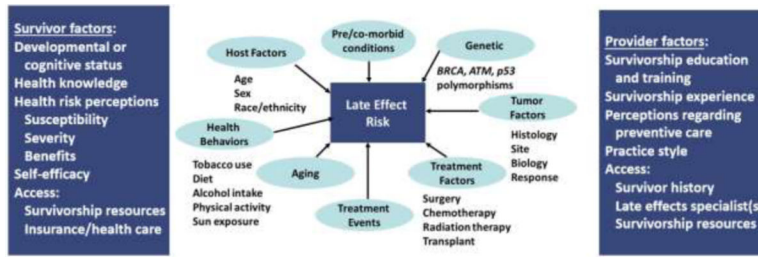


FIGURE 3. A multitude of factors at both the survivor and healthcare provider level influence the risk of morbidity after cancer. Adapted from Hudson et al., Cancer 2005.

TABLE 1.

Health burdens faced by childhood cancer survivors.

Reference	Methods	Data	Author Conclusion
Armstrong et al ³	<ul style="list-style-type: none"> ■ 14,359 5-year survivors from the Childhood Cancer Survivor Study ■ 1st diagnosed when 21 years old ■ 5,604 35 years old (range, 3562 years) at last follow-up ■ Follow-up = median 24.5 years after diagnosis (range, 5–39.3 years) ■ 4,301 siblings. ■ Severe, disabling, life-threatening, and fatal health conditions >5 years from diagnosis classified using CTCAE (version 4.0), grades 3–5 	<ul style="list-style-type: none"> ■ By age 50 years, the cumulative incidence of a severe, disabling, life-threatening, or fatal health conditions was greater among survivors than siblings (53.6%, 95%CI 51.5–55.6; v 19.8%, 95%CI 17.0–22.7). ■ Comparing survivors with siblings, hazard ratios (HR) for severe, disabling, life-threatening, or fatal health conditions were significantly increased within: <ul style="list-style-type: none"> – Age group 5–19 years (HR 6.8, 95%CI 5.5–8.3) – Age group of 20–34 years (HR 3.8, 95%CI 3.2–4.5) – Age group 35 years group (HR 5.0, 95%CI 4.1–6.1) ■ HR for severe, disabling, life-threatening, or fatal health conditions significantly higher among those 35 years versus those 20–34 years old (P=.03). ■ 25.9% of survivors who reached age 35 years without a previous grade 3/4 condition, experienced a subsequent grade 3–5 condition within 10 years, compared with 6.0% of siblings (P<.001) 	<ul style="list-style-type: none"> ■ After fourth decade of life the elevated risk for morbidity and mortality among cancer survivors increases further
Cheung et al ⁴	<ul style="list-style-type: none"> • 5507 adult survivors in the Childhood Cancer Survivor Study who completed a self-report measure of neurocognitive function • 47.1% male • Mean [SD] age at evaluation = 31.8[7.6] years • Mean [SD] years postdiagnosis 23.1 [4.5] years. • Cardiac, pulmonary, and endocrine chronic health conditions were graded using NCI CTCAE (v 4.03) 	<ul style="list-style-type: none"> ■ 1/3 of survivors with grade 2 chronic condition reported impairments in task efficiency and memory ■ “Direct effects” on impaired task efficiency seen with <ul style="list-style-type: none"> – Cranial radiation – Cardiopulmonary conditions ($\beta=0.10$, P=.002; RR=1.27, 95%CI = 1.12–1.44) – Endocrine conditions ($\beta = 0.07$, P=.04; RR=1.14, 95%CI = 1.02–1.28) ■ Effects on memory and emotional regulations seen with <ul style="list-style-type: none"> – Cardiopulmonary conditions [memory (P=.01) and emotional regulation (P=.01). ■ Through endocrine morbidity, thoracic radiation was associated with <ul style="list-style-type: none"> – Impaired task efficiency (P=.01) – Impaired emotional regulation (P=.01) 	<ul style="list-style-type: none"> ■ Non-neurotoxic exposures, such as thoracic radiation, can adversely impact survivors’ neurocognitive function through chronic conditions ■ Management of chronic diseases may mitigate neurocognitive outcomes among aging survivors of childhood cancer
Oancea et al ⁵	<ul style="list-style-type: none"> ■ 1863 adult survivors of childhood cancer ■ Median age at follow up = of 32 years ■ Completed comprehensive medical evaluations ■ Clinically relevant emotional distress assessed using the <i>Brief Symptom Inventory 18</i> and defined as T-scores ≥ 63. ■ Path analysis used to examine associations among identified risk factors 	<ul style="list-style-type: none"> ■ 15.1% of survivors reported elevated global distress ■ Cancer-related pain associated with elevated distress (OR 8.72; 95%CI, 5.32–14.31) ■ Compared to survivors who reported no learning or memory problems, survivors who reported moderate learning or memory problems more likely to have elevated distress (OR 3.27; 95%CI, 2.17–4.93) ■ Path analysis implied cancer-related pain has direct effect on distress symptoms and indirect effect through socioeconomic status and learning or memory problems 	<ul style="list-style-type: none"> Childhood cancer-related morbidities including pain and learning or memory problems appear to be directly and indirectly associated with elevated distress symptoms decades after treatment

Abbreviations: CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; HR, hazard ratio; NCI, National Cancer Institute; OR, odds ratio; RR, relative risk

TABLE 2.

Common or serious late effects by organ system and therapeutic exposure

Organ system/domain (late effect)	Therapeutic exposure*
Brain (neurocognitive deficits)	Methotrexate (intrathecal, high dose intravenous), cytarabine (high dose intravenous)
Eye (cataract)	Busulfan, glucocorticoids (e.g., dexamethasone, prednisone)
Ear (hearing loss)	Carboplatin (myeloablative doses), cisplatin
Peripheral nervous system (neuropathy)	Carboplatin, cisplatin, vinblastine, vincristine
Dental (aplasia, dysplasia, hypoplasia)	Any chemotherapy
Heart (cardiomyopathy)	Anthracyclines (i.e., doxorubicin, daunorubicin, epirubicin, idarubicin), anthraquinone (mitoxantrone)
Lung (interstitial pneumonitis, fibrosis)	Bleomycin, busulfan, carmustine, lomustine
Liver (hepatic dysfunction)	Antimetabolites (i.e., mercaptopurine, methotrexate, thioguanine)
Kidney (renal insufficiency)	Ifosfamide
Gonads (primary hypogonadism)	Alkylating agents (e.g., cyclophosphamide, ifosfamide, busulfan, carmustine, lomustine, melphalan, procarbazine, thiotepa)
Bone (osteopenia)	Glucocorticoids, methotrexate
Secondary malignancy (acute myeloid leukemia, myelodysplasia)	Anthracyclines, alkylating agents, epipodophyllotoxins (i.e., etoposide, teniposide)
Mental health (anxiety, depression, post-traumatic stress)	Any cancer experience

* Radiation to a given area is associated with late effects to the affected organ system, including endocrinopathies (e.g., hypothyroidism, hypogonadism, diabetes), growth and development (e.g., fibrosis, hypoplasia, neurocognitive impairment), premature aging (e.g., atherosclerosis), and second cancers.

TABLE 3.

Profile of late effects risks by common pediatric malignancies

Pediatric malignancy	Contemporary frontline therapeutic modalities*	Potential late effects†
Acute lymphoblastic leukemia & Non-Hodgkin lymphoma	Glucocorticoids Vinca alkaloids Antimetabolites Anthracyclines Alkylating agents	Bone mineral density deficits Peripheral and/or sensory neuropathy Cognitive deficits Cardiomyopathy Gonadal dysfunction/infertility
Acute myeloid leukemia	Anthracyclines Antimetabolites Epipodophyllotoxins	Cardiomyopathy
Ewing sarcoma	Surgical resection Epipodophyllotoxins Alkylating Agents Anthracyclines Vinca alkaloids Primary/metastatic site irradiation	Functional deficits Secondary leukemia Gonadal dysfunction/infertility Cardiomyopathy Peripheral and/or sensory neuropathy Subsequent neoplasms
Hodgkin lymphoma	Glucocorticoids Vinca alkaloids Anthracyclines Alkylating agents Involved node radiation	Bone mineral density deficits Peripheral and/or sensory neuropathy Cardiomyopathy Pulmonary fibrosis Gonadal dysfunction/infertility Hypothyroidism Subsequent neoplasms
Medulloblastoma	Surgical resection Vinca alkaloids Alkylating agents Heavy metals Craniospinal irradiation	Neurologic deficits Peripheral and/or sensory neuropathy Neuroendocrine dysfunction Gonadal dysfunction/infertility Hearing loss Renal dysfunction Cognitive deficits Vasculopathy/stroke
Neuroblastoma	Surgical resection Epipodophyllotoxins Alkylating agents Anthracyclines Heavy metals Immunotherapy	Secondary leukemia Gonadal dysfunction/infertility Hearing loss Renal toxicity Cardiomyopathy Subsequent neoplasms
Osteosarcoma	Surgical resection Antimetabolites Alkylating agents Heavy metals	Functional deficits Renal dysfunction Gonadal dysfunction/infertility Cardiomyopathy Hearing loss
Rhabdomyosarcoma	Surgical resection Vinca alkaloids Anthracyclines Involved site radiation	Peripheral and/or sensory neuropathy Cardiomyopathy Subsequent neoplasms
Wilms tumor	Nephrectomy Vinca alkaloids Anthracyclines Primary/metastatic site irradiation	Renal dysfunction Kyphoscoliosis Peripheral and/or sensory neuropathy Gonadal dysfunction/infertility Cardiomyopathy Subsequent neoplasms

* Exposures listed may vary as therapy is stratified based on clinical and pathological features of pediatric malignancy and early response to therapy.

† The risk of specific late effects varies in magnitude based on specific agents and modalities and dose; survivors with favorable and responsive malignancies may have substantially lower risks for specific late effects due to limited exposures of the agents and modalities listed.

TABLE 4.

Socio-economic burdens faced by childhood cancer survivors.

Reference	Methods	Data	Author Conclusion
Saatci et al ⁶	<ul style="list-style-type: none"> ■ 26 studies ■ 28,434 CCS; 17 814 matched controls [6,582 siblings and 6 population studies from 11 high-income countries, which have similar access to education and years of mandatory schooling] 	<ul style="list-style-type: none"> ■ more likely to remain at compulsory level (OR 1.36, 95%CI 1.26–1.43) ■ CCS less likely to complete secondary (OR 0.93, 95%CI 0.87–1.0) and tertiary level education (OR 0.87, 95%CI 0.78–0.98) ■ CCS more likely to require special educational needs (OR 2.47, 95%CI 1.91–3.20). ■ At secondary level: Irrespective of CNS involvement, compared with cancer-free peers CCS less likely to progress onto secondary (OR 1.77, 95%CI 1.46 to 2.15; OR 1.19, 95%CI 1.00 to 1.42, respectively) ■ At tertiary level: Those with CNS involvement continued to perform worse (OR 0.61, 95%CI 0.55–0.68) but those without appeared to perform similarly to their peers (OR 1.12, 95%CI 1.0–1.25) 	<ul style="list-style-type: none"> ■ Compared with controls, found significant differences in educational attainment in CCS ■ Deficiencies were sustained across different countries, making it an international issue ■ CNS involvement plays a key role in educational achievement ■ Clinicians, teachers and policymakers should advocate for early educational support for survivors
Mader et al ⁷	<ul style="list-style-type: none"> ■ Update a systematic review from 2006 assessing unemployment in adult CCS ■ 56 studies, including 27 controlled studies 	<ul style="list-style-type: none"> ■ ~1/6th of CCS unemployed. ■ Overall meta-analysis of controlled studies: CCS more likely to be unemployed than controls (OR=1.48, 95%CI 1.14–1.93) ■ Elevated OR found in CCS in the US and Canada (OR=1.86, 95%CI 1.26–2.75), as well as in Europe (OR=1.39, 95%CI 0.97–1.97) ■ CCS of brain tumors were more likely to be unemployed (OR=4.62, 95%CI 2.56–8.31) ■ Predictors of unemployment: younger age at study and diagnosis, female sex, radiotherapy, and physical late effects 	<ul style="list-style-type: none"> ■ CCS are at considerable risk of unemployment in adulthood ■ CSS may benefit from psychosocial care services along the cancer trajectory to support labor market integration
Boman et al ⁸	<ul style="list-style-type: none"> ■ National cohort of 1.46 million Swedish residents ■ 1716 CCS diagnosed before 16th birthday, followed up in registries at >25 years of age 	<ul style="list-style-type: none"> ■ CCS of non-CNS cancers had similar education, employment, and income as the general population in adjusted models ■ CCS of CNS tumors: <ul style="list-style-type: none"> – More often had no more than basic (9 years) education (RR 1.80 (95%CI, 1.45–2.23) – Less often attained education beyond secondary school (RR 0.69 95%CI, 0.58–0.81) – Less often were employed (RR 0.85 [95% CI, 0.77–0.94) – Had a predicted net income from work that was lower (P<.001) than in the general population, even after excluding individuals who received economic disability compensation 	<ul style="list-style-type: none"> ■ CNS tumor survivors had poorer social outcomes compared with the general population ■ Outcomes for survivors of other childhood cancers were similar to the general population ■ Highlights importance of improved, safer pediatric CNS tumor treatment protocols
Gunnes et al ⁹	<ul style="list-style-type: none"> ■ 1,212,013 individuals born in Norway during 1965 through 1985 ■ 5440 had cancer diagnosis before age 25 years ■ Follow-up was through 2007 	<ul style="list-style-type: none"> ■ Compared with those in the noncancer group CCS had increased probability of: <ul style="list-style-type: none"> – Receiving governmental financial assistance (men: HR 1.4; 95%CI, 1.3–1.5; women: HR 1.5; 95%CI, 1.3–1.6) – Not being employed (men: HR 1.4; 95%CI, 1.2–1.7; women: HR 1.4; 95%CI, 1.2–1.6) ■ Income discrepancies particularly pronounced for CCS of CNS tumors ■ No difference in representation in higher skilled occupations 	<ul style="list-style-type: none"> ■ Survivors of cancer had increased risk of being economically dependent and unemployed ■ Evident in several tumor groups and most pronounced in female survivors
Wengenroth et al ¹⁰	<ul style="list-style-type: none"> ■ Questionnaire sent to CCS aged 18 years, registered in the Swiss Childhood Cancer Registry (SCCR), diagnosed at age <21 years, who had survived 5 years after diagnosis of the primary tumor ■ Asked questions about education, profession and income and retrieved clinical data from the SCCR ■ 1,506 survivors and 598 siblings 	<ul style="list-style-type: none"> ■ CCS less likely than siblings to have a high monthly income (>4,500 CHF), even after we adjusted for socio-demographic and educational factors (OR=0.46, p<0.001) ■ Lower income than siblings in survivors of: <ul style="list-style-type: none"> – Leukemia (OR=0.40, p<0.001) – Lymphoma (OR=0.63, P=0.040) – CNS tumors (OR=0.22, P<0.001) – Bone tumors (OR=0.24, P=0.003) ■ Survivors who had cranial irradiation, had lower income than survivors who did not have cranial irradiation (OR=0.48, p=0.006) 	<ul style="list-style-type: none"> ■ CCS of various diagnostic groups have lower incomes than siblings even after adjusting for socio-demographic characteristics, education and working hours

Reference	Methods	Data	Author Conclusion
Font-Gonzalez et al ¹¹	<ul style="list-style-type: none"> Medical record linkage of 1283 adult CCS (diagnosed 1966–2001) from a single-centre and two national registers (1999–2011) 25,082 reference persons matched on gender and year of birth Calculated odds (ratios) of specified social outcomes in both groups using multivariable logistic regression Risk factors for the social outcomes analyzed within survivors 	<ul style="list-style-type: none"> Compared with reference persons CCS had higher odds of: <ul style="list-style-type: none"> Not being married (OR 1.2, 95%CI 1.07–1.42) Not living independently (OR 1.7, 95%CI, 1.41–2.00) Using social benefits (OR 2.3, 95%CI, 1.98–2.69) Factors that negatively influenced all social outcomes in CCS: <ul style="list-style-type: none"> Radiotherapy to head and/or neck Original CNS tumor diagnosis 	<ul style="list-style-type: none"> National register data was able to show differences between social outcomes in CCS and the general population Differences especially noted for survivors treated with radiotherapy to head and/or neck and those originally diagnosed with CNS tumors Recommended development and implementation of support strategies to improve social outcomes of CCS
Kirchkoof et al ¹²	<p>Assessed enrollment in supplemental security income (SSI) and social security disability insurance (DI) in 698 long-term CCS vs a comparison group of 210 adults without cancer All had completed a health insurance survey.</p>	<ul style="list-style-type: none"> 13.5% and 10.0% of CCS had ever been enrolled on SSI or DI, respectively, compared with 2.6% and 5.4% of the comparison group Compared with those with mild/moderate or no health conditions the likelihood of receiving assistance increased with: <ul style="list-style-type: none"> 25 Gy cranial radiation doses [RR of current SSI enrollment. = 3.93, 95%CI 2.05–7.56 and RR of current DI enrollment = 3.65, 95%CI 1.65–8.06] Severe/life-threatening conditions [RR of current SSI enrollment = 3.77, 95%CI, 2.04–6.96 and RR of current DI enrollment = 2.73, 95%CI, 1.45–5.14] 	<ul style="list-style-type: none"> Evidence of disability-related financial challenges in CCS More likely to receive public benefits to supplement their incomes than the general population
Huang et al ¹³	<ul style="list-style-type: none"> Examined financial hardship, determinants, and consequences in 2811 long-term CCS Mean age at evaluation = 31.8 years; years postdiagnosis = 23.6 years Financial hardship measured according to (i) material, (ii) psychological, and (iii) coping/behavioral domains. Outcomes included health and life insurance affordability, retirement planning, symptoms, and HRQOL ORs were estimated; all statistical tests were two-sided 	<ul style="list-style-type: none"> Frequency of hardship: <ul style="list-style-type: none"> (i) Material = 22.4%, 95%CI 20.8%–24.0% (ii) Psychological = 51.1%, 95%CI 49.2%–52.9% (iii) Coping/behavioral = 33.0%, 95%CI 31.1%–34.6%) Risk factors across hardship domains included annual household income \$39 999 vs \$80 000 <ul style="list-style-type: none"> (i) Material OR 3.04, 95%CI 2.08–4.46 (ii) Psychological OR 3.64, 95%CI 2.76–4.80 (iii) Coping/behavioral OR 4.95, 95%CI 3.57–6.86 than high school attainment vs college graduate or above: <ul style="list-style-type: none"> (i) Material OR 2.22, 95%CI = 1.45–3.42 (ii) Psychological OR 1.75, 95%CI, 1.18–2.62 (iii) Coping/behavioral OR 2.05, 95%CI = 1.38–3.06 Association with higher material hardship (all p<.05) <ul style="list-style-type: none"> Myocardial infarction Peripheral neuropathy Subsequent neoplasm Seizure, stroke Reproductive disorders Amputation Upper gastrointestinal disease Hardship across three domains associated with <ul style="list-style-type: none"> Somatization, anxiety and depression (all P<.001) Suicidal ideation (all P<.05) Difficulty in retirement planning (all P<.001) Survivors with hardship had <ul style="list-style-type: none"> Statistically significantly lower HRQOL (all P<.001) Sensation abnormality (all P<.001) Pulmonary symptoms (all P<.05) Cardiac symptoms (all P<.05) 	<ul style="list-style-type: none"> Substantial proportion of CCS experience financial hardship. Vulnerable sociodemographic status and late effects associated with hardship CCS with financial hardship had an increased risk of symptom prevalence and impaired HRQOL
Kunin-Baston et al ¹⁴	<ul style="list-style-type: none"> Long-term follow-up questionnaire of 6,047 adult CCS and 2,326 siblings all 25 years of age Assessed adaptive, neurocognitive, and psychological functioning, as well as demographic and health status Multivariable logistic regression analyses and 	<ul style="list-style-type: none"> CCS (n = 1063; 17.7%) more than twice as likely to live dependently than siblings (n = 206, 8.7%), survivors were (OR 2.07, 95%CI 1.77–2.42) CCS who had CNS tumors significantly less likely to live independently than those who had Hodgkin lymphoma (OR 0.13, 95%CI 0.10–0.18) or leukemia (OR 0.29, 95%CI 0.23–0.27) Other risk factors for reduced independent living: <ul style="list-style-type: none"> Cranial radiation (< 24Gy OR 0.76, 95%CI 0.62–0.93; >24Gy OR 0.31, 95%CI 0.24–0.41) 	<ul style="list-style-type: none"> Adult CCS are less likely to live independently as adults especially those who experience neurocognitive, psychological, or physical late effects

Reference	■ Methods	■ Data	■ Author Conclusion
	structural equation modeling (SEM) used to identify predictors of independent living	<ul style="list-style-type: none"> – Use of neuroleptic, anticonvulsant, or psychostimulant medication (OR 0.32, 95% CI 0.24–0.43) – Attention and processing speed problems (OR 0.58, 95% CI 0.47–0.71) – Poor physical functioning (OR 0.49, 95% CI 0.38–0.63) – depression (OR 0.68, 95% CI 0.53–0.88) – Racial/ethnic minority status (OR 0.39, 95% CI 0.30–0.51) • SEM demonstrated that neurocognitive functioning had both direct effects on independent living status, and indirect effects through use of neurologically directed medication, depression, and poor mental health 	
Ness et al ¹⁵	<ul style="list-style-type: none"> • Demographic information used to classify social roles • Medical Outcomes Survey 36–Item ShortForm Health Survey to ascertain HRQOL 	<ul style="list-style-type: none"> • Deficits reported amongst CCS <ul style="list-style-type: none"> – 18.1% deficits in physical performance – 10.5% deficits in emotional health – 14.0% deficits in executive function • CCS with physical performance, executive function, or emotional health deficits were less likely to be employed, married, or have incomes >\$20,000/year than those who reported no limitations • Limitations in executive function or emotional health associated with no health insurance • Limitations in any activity domain associated with poor HRQOL Emotional health limitations had the most impact <ul style="list-style-type: none"> – Physical performance summary: OR 3.18 – Mental health: OR 25.8 	<ul style="list-style-type: none"> • CSS report long-term poor physical, mental, or general health that negatively impact role attainment and HRQOL

Abbreviations: CCS, childhood cancer survivors; CI, confidence interval; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; HR, hazard ratio; HRQOL, health-related quality of life; NCI, National Cancer Institute; OR, odds ratio; RR, relative risk

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TABLE 5.

Comparison of the cumulative incidence versus mean cumulative count method

Cumulative incidence	Mean cumulative count
Considers only the first occurrence of the “event of interest” for each individual in the analysis	Provides a summarization of all “events of interest” that occur in the population by a given time, not just the first event for each subject
Because subsequent occurrences of the same event are not included, this metric does not describe the total burden of events in a population	Because this metric considers all events during the period of observation, it can be a more relevant measure of <i>overall disease burden</i> of the “event of interest” in a population “at risk”
Considered reasonable if the first occurrence of the “event of interest” changes underlying risk and/or biology of any subsequent event	Assumes the first occurrence of the “event of interest” does not meaningfully change the underlying risk and/or biology of any subsequent event
Cumulative probability of the first event of interest depends on survival free of <i>both</i> the event of interest and the competing-risk event	Survival probability depends only on survival free of a competing-risk event.
A probability – ranges from 0–1	Not a probability. Not confined by 0–1 range, it can be any positive number
Estimates the proportion of individuals who experience the event of interest	Estimates the average number of events per person in the population

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TABLE 6.

Genetic susceptibility to anthracycline cardiomyopathy/cardiotoxicity (ACT)

Gene / Variant	Methods	Results	Comment / Conclusion
<p>RARG³⁶ The retinoic acid receptor (RAR) is a nuclear receptor that can also act as a transcription factor. RAR is activated by both all-trans retinoic acid and 9-cis retinoic acid. There are three RARs: RARα, RARβ, and RARγ, encoded by the <i>RARA</i>, <i>RARB</i> and <i>RARG</i> genes, respectively.</p>	<ul style="list-style-type: none"> • Genome-wide association study in 280 CCS of European ancestry with independent replication in similarly treated cohorts of 96 European and 80 non-European CCS 	<ul style="list-style-type: none"> • Identified a nonsynonymous variant (rs2229774, p.Ser427Leu) in RARG highly associated with ACT [$P=5.9 \times 10^{-8}$, OR 4.7 (95%CI 2.7–8.3)]. 	<ul style="list-style-type: none"> • RARG may confer susceptibility to ACT in CCSs. • Variant alters RARG function, leading to derepression of the key ACT genetic determinant Top2b
<p>UGT1A6 and SLC28A3³⁷ • UGT1A6: UDP-glucuronosyltransferase 1–6 is an enzyme of the glucuronidation pathway that transforms small lipophilic molecules into watersoluble, excretable metabolites. This gene is part of a complex locus that encodes several UDP-glucuronosyltransferases. UDP-glucuronosyltransferase is also responsible for the inactivation of drugs. • SLC28A3: The human concentrative nucleoside transporter CNT3 (SLC28A3) plays an important role in mediating the cellular entry of a broad array of physiologic nucleosides and synthetic anticancer nucleoside analog drugs</p>	<ul style="list-style-type: none"> • 23 variants tested for association with ACT in an independent cohort of 218 patients 	<ul style="list-style-type: none"> • Confirmed association of rs17863783 in UGT1A6 and ACT ($P = 0.0062$, OR 7.98). • Additional evidence for association of rs7853758 ($P = 0.058$, OR 0.46) and rs885004 ($P = 0.058$, OR 0.42) in SLC28A3 was found (combined $P=1.6 \times 10^{-5}$ and $P=3.0 \times 10^{-5}$, respectively). 	<ul style="list-style-type: none"> • Validation of variants in SLC28A3 and UGT1A6 as genetic markers predictive of ACT in CCSs • An improved prediction model using replicated genetic variants as well as clinical factors discriminated significantly better between cases and controls than clinical factors alone
<p>SLC22A17 and SLC22A7³⁸ • SLC22A17: Polyspecific organic cation transporter in liver, kidney, intestine, and other organs. Critical for eliminating endogenous small organic cations and wide array of drugs and environmental toxins. One of three similar cation transporter genes located in a cluster on chromosome 6. • SLC22A7: Involved in sodium-independent transport and excretion of organic anions some potentially toxic. It's a membrane protein localized to basolateral membrane of kidney. Alternatively, spliced transcript variants encoding different isoforms exist</p>	<ul style="list-style-type: none"> • Two cohorts treated for childhood cancer ($n = 344$ and 218, respectively) were genotyped for 4578 SNPs in drug ADME and toxicity genes 	<ul style="list-style-type: none"> • Significant associations identified in SLC22A17 (rs4982753; $P=0.0078$) and SLC22A7 (rs4149178; $P=0.0034$), with replication in the second cohort ($P=0.0071$ and 0.047, respectively) 	<ul style="list-style-type: none"> • Genetic variants in SLC22A17 and SLC22A7 were associated with ACT in CSSs • SLC22A17 and SLC22A7 variants improved a genotype-guided risk prediction model, which could improve patient risk stratification
<p>CELF4³⁹ • CUGBP Elav-like family member 4 (CELF4) also known as bruno-like protein 4 (BRUNOL4) is encoded by the CELF4 • Members of this protein family regulate pre-mRNA alternative splicing and may also be involved in mRNA editing, and translation.</p>	<ul style="list-style-type: none"> • Genome-wide association study in CCSs with/without cardiomyopathy. SNPs surpassing a prespecified threshold for statistical significance were independently replicated 	<ul style="list-style-type: none"> • No SNP was marginally associated with ACT • SNP rs1786814 on CELF4 gene passed significance cutoff for gene-environment interaction ($P_{ge}=1.14 \times 10^{-5}$). In patients with A allele, cardiomyopathy infrequent and not dose related • If exposed to >300 mg/m² anthracyclines, rs1786814 GG genotype conferred 10.2-fold (95%CI, 3.8- to 27.3-fold; $P < .001$) cardiomyopathy risk compared with GA/AA genotypes and exposure 300 mg/m² • Gene-environment interaction successfully replicated in independent set of ACT cases 	<ul style="list-style-type: none"> • Modifying effect of a polymorphism of CELF4 (rs1786814) on the dose-dependent association between anthracyclines and cardiomyopathy; possibly through pathway involving expression of abnormally spliced TNNT2 variants • Coexistence of 1 cTnT variant results in temporally split myofibrillar response to calcium, and decreased contractility • Analysis of TNNT2 splicing variants in healthy human hearts suggested an association between the rs1786814 GG genotype and coexistence of 1 TNNT2 splicing variant (90.5% GG v 41.7% GA/AA; $P=0.005$)

Gene / Variant	Methods	Results	Comment / Conclusion
<p>HAS3⁴⁰ HAS3 (Hyaluronan 3): Encodes a protein involved in synthesis of hyaluronic acid, a major constituent of the extracellular matrix. This gene is a member of the NODC/HAS gene family. Compared to the proteins encoded by other members of this gene family, this protein appears to be more of a regulator of hyaluronan synthesis.</p>	<ul style="list-style-type: none"> Used two-stage design, to investigate host susceptibility to ACT by using the ITMAT/Broad CARE cardiovascular SNP array to profile common SNPs in 2,100 genes considered relevant to de novo cardiovascular disease 	<ul style="list-style-type: none"> Using matched case-control design (93 cases, 194 controls), identified a common SNP, rs2232228, in HAS3 gene that exerts a modifying effect on anthracycline dose-dependent cardiomyopathy risk ($P=5.3 \times 10^{-7}$) Among individuals with rs2232228 GG genotype, cardiomyopathy infrequent and not dose related In individuals exposed to >250 mg/m² anthracyclines, rs2232228 AA genotype conferred 8.9-fold (95%CI, 2.137.5-fold; $P=0.003$) increased risk of cardiomyopathy compared with GG genotype HAS3 mRNA levels in healthy hearts lower among individuals with AA compared with GA genotypes ($P=0.09$) 	<ul style="list-style-type: none"> HAS3 produces hyaluronic acid a ubiquitous component of the extracellular matrix that plays role in tissue remodeling and is known to reduce ROS-induced cardiac injury. High cardiomyopathy risk associated with AA genotype could be due to inadequate remodeling and/or inadequate protection of the heart from ROS-mediated injury after high anthracycline exposure
<p>CBR3⁴¹ CBR3: Carbonyl reductases (CBRs) catalyze reduction of anthracyclines to cardiotoxic alcohol metabolites. Polymorphisms in CBR1 and CBR3 influence synthesis of these metabolites.</p>	<ul style="list-style-type: none"> 170 CCSs with cardiomyopathy (patient cases) were compared with 317 survivors with no cardiomyopathy (controls; matched on cancer diagnosis, year of diagnosis, length of follow-up, and race/ethnicity) using conditional logistic regression techniques. 	<ul style="list-style-type: none"> Dose-dependent association observed between cumulative anthracycline exposure and cardiomyopathy risk: <ul style="list-style-type: none"> – 0 mg/m²: reference; – 1 to 100 mg/m²: OR 1.65 – 101 to 150 mg/m²: OR 3.85; 151 to 200 mg/m²: OR 3.69; – 201 to 250 mg/m²: OR 7.23; – 251 to 300 mg/m²: OR 23.47; – >300 mg/m²: OR 27.59; P(trend) < .001 No increased risk of cardiomyopathy after exposure to low- to moderate-dose ANTH (1–250 mg/m²) with variant A allele (CBR1:GA/AA and/or CBR3:GA/AA) Exposure to low- to moderate-dose anthracyclines increased cardiomyopathy risk among individuals with CBR3 V244M homozygous G genotypes (CBR3:GG), when compared with individuals with CBR3:GA/AA genotypes unexposed to anthracyclines (OR 5.48; $P=0.003$), as well as exposed to low- to moderate-dose anthracyclines (OR 3.30; $P=0.006$) <250 mg/m² anthracyclines associated with increased cardiomyopathy risk, irrespective of CBR genotype status 	<ul style="list-style-type: none"> ACT risk increased at doses as low as 101 to 150 mg/m² Homozygosis for G allele in CBR3 contributes to increased cardiomyopathy risk with low- to moderate-dose anthracyclines, such that there seems to be no safe dose for patients homozygous for the CBR3 V244M G allele

Abbreviations: 95%CI, 95% confidence interval; Anth, anthracycline; ACT, anthracycline-induced cardiotoxicity; OR, odds ratio; ROS, reactive oxygen species; SNPs, single-nucleotide polymorphisms

TABLE 7.

Genetic susceptibility to subsequent malignant neoplasms

Gene / Variant	Methods	Results	Comment / Conclusion
<p>PRDM1⁴² PRDM1 encodes PR domain zinc finger protein 1 also known as BLIMP-1. Increased Blimp-1 expression in immune system cells leads to proliferation and differentiation of antibody secreting plasma cells. Blimp-1 is also considered a 'master regulator' of hematopoietic stem cells.</p>	<ul style="list-style-type: none"> Discovery set was 100 CCSs individuals treated for HL who subsequently developed SMNs and 89 individuals treated for HL who did not develop SMNs. European descent with diagnosis of HL at 10–20 years of age Treated similarly with 25–44 Gy RT chemotherapy with an alkylating agent Radiation exposure was to the site at which the subsequent SMN developed Distribution and frequency of sites exposed to RT similar between cases and controls Controls from all HL cases without SMN followed for 27 years treatment for HL 	<ul style="list-style-type: none"> Three SNPs achieved genome-wide significance: rs4946728, rs1040411 and rs8083533 rs4946728 ($P=1.09 \times 10^{-8}$, $OR_{allelic} = 4.22$; 95% CI = 2.53–7.05). and rs1040411 mapped to chromosome 6q21, between <i>ATG5</i> and <i>PRDM1</i>. rs8083533 mapped to 18q11.2, intronic to <i>TAF4B</i> (encoding transcription initiation factor TFIID subunit 4B) ($P=4.98 \times 10^{-8}$, $OR_{allelic} 3.78$, 95% CI 2.31–6.18) Gender, age at diagnosis, year of HL diagnosis, gonadal RT (in females) and alkylating chemotherapy exposure, had no effect on the observed associations 	<ul style="list-style-type: none"> Survivors of pediatric HL are at risk for RT-induced SMNs Two variants at chromosome 6q21 associated with SMNs in survivors of HL treated with RT as children but not as adults. The variants comprise a risk locus associated with decreased basal expression of <i>PRDM1</i> and impaired induction of the <i>PRDM1</i> after RT Data suggest gene-exposure interaction that may implicate <i>PRDM1</i> in the etiology of RT-induced SMNs.
<p>FGFR2⁴³ FGFR2 also known as CD332 (cluster of differentiation 332) is a receptor for fibroblast growth factor. Member of fibroblast growth factor receptor family. Extracellular portion interacts with fibroblast growth factors, setting in motion cascade of downstream signals, ultimately influencing mitogenesis and differentiation. <i>FGFR2</i> is a high-affinity receptor for acidic, basic and/or keratinocyte growth factor.</p>	<ul style="list-style-type: none"> 2 case-control series: Discovery: 449 women with HL treated with supradiaphragmatic RT in UK at age <36 years: 140 had BC after HL treatment (the "cases") and 309 had had no solid cancer after HL (the "controls") Replication: 244 female Dutch HL patients treated with supradiaphragmatic RT at age <41 years: 92 cases and 152 controls. 	<ul style="list-style-type: none"> Genotype frequencies of rs1219648 significantly different between cases vs. controls. Overrepresentation of the minor, G allele, in HL patients with BC ($OR 1.73$; $P=0.00273$). Association dose-dependent; highest risks if homozygous for G allele $OR >$ for BC in relation to <i>FGFR2</i> genotype in the general population (1.26 per allele) Effect greater if <20 years when first treated ($OR 1.70$, 95% CI 1.16–2.50) than 20 years ($OR 1.48$, 95% CI 1.09–2.00), and if had not received an alkylating agent or 5-Gy pelvic radiotherapy 	<ul style="list-style-type: none"> Women treated at young ages with supradiaphragmatic RT for HL have a highly increased risk of BC. rs1219648, which annotates the <i>FGFR2</i> gene associated with risk in discovery and replication (combined per-allele $OR 1.59$, 95% CI 1.26–2.02; $P=0.0001$) Evidence genetic variation in <i>FGFR2</i> influences RT-induced BC risk.
<p>PROX1; TAGLN⁴⁴ PROX1: Transcription factor involved in cell fate determination, gene transcriptional regulation and progenitor cell regulation in a number of organs. Plays critical role in embryonic development and functions as a key regulatory protein in neurogenesis and the development of other organs. TAGLN: Encodes transgelin, a transformation and shapechange sensitive actin crosslinking/gelling protein found in fibroblasts and smooth muscle. Down-regulation of expression may be early and sensitive marker of transformation. Functional role unclear.</p>	<ul style="list-style-type: none"> Genome-wide association study of BC in female CCS, pooling two cohorts with detailed treatment data and systematic, long-term follow-up 207 survivors who developed breast cancer and 2774 who had not developed any subsequent neoplasm as of last follow-up 16 958 466 high-quality variants for analysis 	<ul style="list-style-type: none"> CCS who received exposure to breast of 10 gray, a locus on 1q41 was associated with subsequent BC risk (rs4342822, nearest gene <i>PROX1</i>, risk allele frequency in control subjects [RAF controls] = 0.46, hazard ratio 1.92, 95% CI 1.49–2.44, $P=7.09 \times 10^{-9}$) Potentially promising associations for rs74949440, 11q23, <i>TAGLN</i>, RAF controls = 0.02, $P=5.84 \times 10^{-8}$ 	<ul style="list-style-type: none"> Strong evidence germline genetics outside high-risk syndromes could modify effect of RT on BC risk in CCSs
<p>HTR2A⁴⁵ HTR2A encodes one of the receptors for serotonin, a multifunctional</p>	<ul style="list-style-type: none"> GWAS of subsequent BCC in European CCS treated with RT Evaluated genome-wide significant SNPs ($P < 5 \times 10^{-8}$) 	<ul style="list-style-type: none"> Discovery cohort did not identify variants reaching genome-wide significance; however, 14 SNPs on 	<ul style="list-style-type: none"> Results suggest <i>HTR2A</i>-BCC association among CCS treated with RT may be more pronounced in individuals <40

Gene / Variant	Methods	Results	Comment / Conclusion
neurotransmitter with roles in many physiologic processes such as sleep, hormone secretion, and appetite	Discovery cohort (401 and 2,330 control); independent cohort (97 case patients and 1,082 control)	<p><i>HTR2A</i> showed strongest associations (adjusted HRs ~1.50; $P < 1 \times 10^{-6}$)</p> <ul style="list-style-type: none"> • Further studies showed genome-wide significance for 11/14 <i>HTR2A</i> SNPs • Strongest association for rs633737 (HR = 2.25; $P = 5.99 \times 10^{-9}$, P-value based on 100 million permutations [$P_{perm} < 1 \times 10^{-8}$]) • High among leukemia and HL survivors • Association of <i>HTR2A</i> with BCC attenuated (HRs 1.30–1.36) and/or not statistically significant ($P > 0.51$) among survivors not in low-risk subgroup/ periods (<40 yrs of age; treated when 10 yrs) 	<p>years old and those 10 years old when treated</p> <ul style="list-style-type: none"> • Possibly because key nongenetic factors, (RT exposure, years sun exposure, and aging) are less influential relative to the older age of survivors treated at a younger age (10 years old).
60 genes associated with autosomal dominant cancer predisposition syndromes with moderate to high penetrance⁴⁶	<ul style="list-style-type: none"> • WGS performed on samples from CCS 5 years since initial cancer diagnosis. • Looked for germline mutations in 60 genes known to be associated with autosomal dominant cancer predisposition syndromes with moderate to high penetrance 	<ul style="list-style-type: none"> • 3,006 survivors (53% male; median age, 35.8 years [range, 7.1 to 69.8 years]); 56% received RT, 1,120 SMNs diagnosed in 439 survivors (14.6%), and 175 P/LP mutations identified in 5.8% (95% CI 5.0–6.7%) • Among survivors who received RT mutations associated with significantly increased rates of; <ul style="list-style-type: none"> • BC (RR 13.9, 95% CI, 6.0–32.2) • Sarcoma (RR 10.6, 95% CI, 4.3–26.3) • Among survivors who did not received RT mutations associated with significantly increased rates of; <ul style="list-style-type: none"> • Any SMN (RR 4.7, 95% CI, 2.4–9.3) • BC (RR 7.7, 95% CI, 2.4–24.4) • Nonmelanoma skin cancer (RR 11.0, 95% CI, 2.9–41.4) • 2 histologically distinct SMNs (RR 18.6, 95% CI, 3.5–99.3) 	<ul style="list-style-type: none"> • Findings support referral of all CCSs for potential clinical genetic testing, with priority for survivors who did not receive RT and have any SMN and for those with BC or sarcoma in the field of prior RT

Abbreviations: 95%CI, 95% confidence interval; BC, breast cancer; BCC, basal cell carcinoma; CCSs, childhood cancer survivors; GWAS, Genome-wide association study; HL, Hodgkin lymphoma; OR, odds ratio; P/LP, pathogenic/likely pathogenic; RT, radiation therapy; SMN, second malignant neoplasms; SNPs, single-nucleotide polymorphisms; WGS, whole genome sequencing

TABLE 8.

Genetic susceptibility to reproductive health issues

Gene / Variant	Methods	Results	Comment / Conclusion
BRSK1 ⁴⁷ BRSK1 (BR serine/threonine kinase 1) is a serine/threonine-protein kinase that plays key role in polarization of neurons and centrosome duplication	<ul style="list-style-type: none"> • Single-center pilot study of 176 adult female Caucasian CCS with serum AMH levels as a marker of ovarian reserve • Studied SNPs previously reported associated with age at natural menopause: BRSK1 (rs1172822), ARHGEF7 (rs7333181), MCM8 (rs236114), PCSK1 (rs271924), IGF2R (rs9457827) and TNF (rs909253) 	CT genotype of rs1172822 in BRSK1 gene negatively associated with serum AMH levels (OR 3.15, 95%CI 1.35–7.32, P=0.008) and significantly associated with the predicted age at menopause (P=0.04) Other 5 SNPs not associated with serum AMH levels	Previously identified SNPs associated with age at menopause in healthy women may have an effect on onset of menopause in female CCS.
NPY2R ⁴⁸ NPY2R (Neuropeptide Receptor 2 gene) belongs to a family of G-protein coupled receptors activated by a group of closely related peptide hormones. These neuropeptide Y receptors control diverse behavioral processes including appetite, circadian rhythm and anxiety. Activated neuropeptide receptors release G ₁ subunit from the heterotrimeric G protein complex and this in turn inhibits production of the second messenger cAMP	<ul style="list-style-type: none"> • GWAS of 779 female CCSs to identify SNPs associated with clinically diagnosed PM (defined as menopause <40 years) Analyses adjusted for cyclophosphamide equivalent dose of alkylating agents and ovarian RT dose • Replication using self-reported PM in 1624 survivors p in the Childhood Cancer Survivor Study (CCSS) 	<ul style="list-style-type: none"> • PM clinically diagnosed in 30 (3.8%) participants • 13 SNPs upstream of NPY2R associated with prevalence of PM (minimum P=3.3 × 10⁻⁷ for rs9999820, all P< 10⁻⁵) • Homozygous carrier of a haplotype formed by 4/13 SNPs associated with markedly elevated PM prevalence if exposed to ovarian RT (OR 25.89, 95%CI 6.18–138.31, P=8.2 × 10⁻⁶); replicated in the independent second cohort 	<ul style="list-style-type: none"> • NPY2R haplotype captures majority of clinically diagnosed PM cases • Evidence from bioinformatics suggests the haplotype alters regulation of NPY2R transcription, possibly affecting PM risk through neuroendocrine pathways
ERα and ERβ ⁴⁹	<ul style="list-style-type: none"> • 51 SNP markers of 12 different haplotype blocks in the AR, ERα and ERβ genes examined in 127 CCS 	<ul style="list-style-type: none"> • Markers of one specific haplotype block of ERα (rs2207396, rs9340958, rs9340978) associated with increased risk of azoospermia • Compared with GG genotype, patients heterozygous for A allele in rs2207396 had significantly increased risk of azoospermia [OR 3.8; 95%CI: 1.5–9.5; P=0.008], and even higher if treated with alkylating agents (OR 8.8; 95%CI 2.1–36; P=0.004) 	<ul style="list-style-type: none"> • Genetic markers of high risk of post-treatment azoospermia may help identify boys to whom preservation of testicular tissue before cancer therapy should be offered

95%CI, 95% confidence interval; AR, androgen receptor; CCSs, childhood cancer survivors; ER, estrogen receptor; GWAS, Genome-wide association study; OR, odds ratio; PM, premature menopause; RT, radiation therapy; SNPs, single-nucleotide polymorphisms

TABLE 9.

Molecularly targeted agents being used or under consideration for pediatric cancers (adapted and updated from Chow et al., J Clin Oncol 2018)

Target(s)	Drug(s)	Notable toxicities*
ALK/ROS	Ceritinib Crizotinib Emsartinib Lorlatinib	Arrhythmia Dyslipidemia (lorlatinib) Hyperglycemia (ceritinib) Hallucinations / psychiatric (lorlatinib) Neuropathy/neuromuscular Pulmonary embolism (crizotinib) Respiratory Vision changes
BCR/ABL, KIT, PDGFR	Dasatinib Imatinib Nilotinib Ponatinib	Cardiac dysfunction Edema, effusions Growth & stature* Pulmonary hypertension (dasatinib) Thyroid dysfunction Vascular events, including myocardial ischemia, peripheral arterial occlusion, and stroke (ponatinib)
BRAF	Dabrafenib Vemurafenib	Hyperglycemia (dabrafenib) New acute development of skin cancers QT-prolongation (vemurafenib) Radiation sensitivity
CD3	Blinatumomab	B cell aplasia (CAR T cells)* Cytokine release syndrome Neurotoxicity
CD19	Blinatumomab Chimeric antigen receptor (CAR) T cells	Same as with CD3-targeted agents above
CD20	Rituximab	B cell aplasia
CD30	Brentuximab vedotin	Neuropathy Progressive multifocal leukoencephalopathy
CD33	Gemtuzumab ozogamicin	Hepatotoxicity, sinusoidal obstruction syndrome
CDK/cyclin (cell cycle)	Palbociclib Ribociclib	QT-prolongation (ribociclib)
EZH2	Tazemetostat	Limited experience to date
GD2	Dinutuximab Hu3F8 Hu14.18K322A	Capillary leak syndrome Neuropathic pain Reversible posterior leukoencephalopathy
HDAC (histone deacetylase)	Entinostat Fimepinostat Panobinostat Romidepsin Vorinostat	Arrhythmia / myocardial infarction Pulmonary embolus (vorinostat) <i>Limited experience for entinostat, fimepinostat</i>
MEK/MAPK	Binimetinib Cobimetinib Selumetinib Trametinib	Cardiac dysfunction Skin toxicity Vision changes, retinopathy
mTOR	Everolimus Sirolimus Temsirolimus ABI-009 (Nab-Rapamycin) LY3023414	Dyslipidemia Hyperglycemia

Target(s)	Drug(s)	Notable toxicities*
PD-1, PDL-1, CTL4 (immune checkpoint)	Atezolizumab Avelimumab Cemiplimab Durvalumab Ipilimumab Nivolumab Pembrolizumab	Auto-immune/inflammatory, including: Endocrinopathies Myocarditis Neurotoxicity Pneumonitis
PI3K	Fimepinostat LY3023414	Hyperglycemia
TRK	Entrectinib Larotrectinib	Limited experience to date
VEGF, VEGFR, PDGFR, RET	Axitinib Bevacizumab Cabozantinib Lenvantinib Pazopanib Sorafenib Vandetanib	Cardiac dysfunction Hemorrhage, impaired wound healing Hepatotoxicity (pazopanib) Hypertension, proteinuria Intestinal perforation/fistula (bevacizumab) Thromboembolism Thyroid dysfunction (axitinib, pazopanib, sorafenib)

* Toxicities that may persist well after cessation of therapy, or develop later

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