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## Long-Term Follow-up Care for Childhood, Adolescent, and Young Adult Cancer Survivors

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### Abstract

Progress in therapy has made survival into adulthood a reality for most children, adolescents, and young adults with a cancer diagnosis today. Notably, this growing population remains vulnerable to a variety of long-term therapy-related sequelae. Systematic ongoing follow-up of these patients is, therefore, important to provide for early detection of and intervention for potentially serious late-onset complications. In addition, health counseling and promotion of healthy lifestyles are important aspects of long-term follow-up care to promote risk reduction for physical and emotional health problems that commonly present during adulthood. Both general and subspecialty health care providers are playing an increasingly important role in the ongoing care of childhood cancer survivors, beyond the routine preventive care, health supervision, and anticipatory guidance provided to all patients. This report is based on the guidelines that have been

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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developed by the Children's Oncology Group to facilitate comprehensive long-term follow-up of childhood, adolescent, and young adult cancer survivors ([www-survivorshipguidelines.org](http://www-survivorshipguidelines.org)).

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## BACKGROUND INFORMATION

Cancer is diagnosed in approximately 20 000 children and 80 000 adolescents and young adults annually in the United States.<sup>1</sup> Before 1970, almost all children, adolescents, and young adults with cancer died from their primary disease. However, rapid improvements in multimodal treatment regimens (chemotherapy, radiation therapy, surgery, and immunotherapy), coupled with aggressive supportive-care regimens, have resulted in survival rates that continue to increase. The current estimated 5-year overall survival rate for childhood, adolescent, and young adult malignancies exceeds 80%,<sup>2</sup> which translates into increasing numbers of long-term survivors, now estimated to approach 500 000 in the United States, who may seek ongoing care from community primary and subspecialty providers.<sup>3</sup> The Childhood Cancer Survivor Study (CCSS), the largest and most extensively characterized cohort of 5-year childhood cancer survivors in North America, reported that survivors receive most of their care from primary care providers.<sup>4</sup> Furthermore, the proportion of survivors reporting survivor-focused care that includes regular risk-based surveillance and prevention strategies related to their prior cancer and its treatment decreases with increasing time from cancer diagnosis. Thus, primary care providers (pediatricians, family practitioners, internists, practitioners trained in internal medicine and pediatrics (med-peds), and advanced practice providers) are likely to have an increasingly vital role in caring for this rapidly growing population.

## STATEMENT OF PROBLEM

Cancer and its treatment may result in a variety of physical and psychosocial effects that predispose long-term survivors to excess morbidity and early mortality when compared with the general population.<sup>5-10</sup> Virtually every organ system can be affected by the chemotherapy, radiation, surgery, and/or immunotherapy required to achieve cure. Late complications of treatment may include problems with organ function, growth and development, neurocognitive function and academic achievement, and the potential for additional cancers. Cancer and its treatment also have psychosocial consequences that may adversely affect family/peer relationships, educational attainment (both formal and practical knowledge gained from real-world experience), vocational and employment opportunities, and insurance and health care access. In addition, survivors may experience troubling body image changes or suffer from chronic symptoms (eg, fatigue, dysomnia, pain) that adversely affect emotional health and quality of life. A young person's and family's lives are forever changed when touched by the cancer experience, and it is critical to provide rehabilitation services to survivors who highly value good health and unrestricted performance status. Equally important is reaching out to young adult survivors who may be separated from their families and face more challenges in adhering to healthy lifestyles and accessing health care services.

Late effects after childhood, adolescent and young adult cancer are common. Two of every 3 childhood cancer survivors will develop at least 1 late-onset therapy-related complication; in 1 of every 4 cases, the complication will be severe or life threatening.<sup>6,11</sup> Among clinically ascertained cohorts, the prevalence of late effects is higher because of the subclinical and undiagnosed conditions detected by screening and surveillance measures.<sup>8</sup> Childhood, adolescent, and young adult cancer survivors, therefore, require ongoing comprehensive long-term follow-up care to optimize long-term outcomes by successfully monitoring for and treating the late effects that may occur as a result of previous cancer therapies as well as anticipatory guidance and health promotion efforts addressing primary and secondary prevention of chronic disease. Access to care and services that address health risks predisposed by cancer and its treatment can optimize achievement of independent living, employment, and insurance access, which is particularly important for a population at risk of multimorbidity.

Because health risks associated with cancer are unique to the age at treatment and specific therapeutic modality, it is important that follow-up evaluations and health screening be individualized based on treatment history. To facilitate comprehensive and systematic follow-up of childhood, adolescent, and young adult cancer survivors, the Children's Oncology Group (COG) organized exposure-based health screening guidelines. This clinical report presents pediatricians and other health care professionals with guidance for providing high-quality long-term follow-up care and health supervision for survivors of pediatric, adolescent, and young adult malignancies by incorporating long-term follow-up guidelines developed by the COG into their practice<sup>12</sup> and by maintaining ongoing interaction with oncology subspecialists to facilitate communication regarding any changes in follow-up recommendations specific to the cancer survivors under their care.

## METHODS: DEVELOPMENT OF LONG-TERM FOLLOW-UP GUIDELINES

The COG is a cooperative clinical trials group supported by the National Cancer Institute with more than 200 member institutions. In January 2002, at the request of the Institute of Medicine (now the National Academy of Medicine), a multidisciplinary panel within COG initiated the process of developing comprehensive risk-based, exposure-related recommendations for screening and management of late treatment-related complications potentially resulting from therapy for childhood, adolescent, and young adult cancers. The resulting comprehensive resource, the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (COG LTFU Guidelines)*,<sup>12</sup> is designed to raise awareness of the risk of late treatment-related sequelae to facilitate early identification and intervention for these complications, standardize follow-up care, improve quality of life, and provide guidance to health care professionals, including pediatricians, who supervise the ongoing care of young cancer survivors.

The *COG LTFU Guidelines* are designed for use in asymptomatic childhood, adolescent, and young adult survivors presenting for routine health maintenance at least 2 years after completion of cancer-directed therapy (eg, surgery, chemotherapy, radiation, immunotherapy) whether the survivor is receiving care in a pediatric cancer, a specialized adolescent-young adult program, an adult-focused oncology program, a long-term follow-up

program, or community primary care practice. The guidelines are not designed for primary cancer-related surveillance, which is an important component of survivorship care that generally continues under the guidance of the treating oncologist throughout the period when the patient remains at highest risk of relapse but may ultimately be transferred to community primary care providers (pediatricians, family physicians, internists, practitioners trained in internal medicine and pediatrics (med-peds), and advanced practice providers). This period of risk varies depending on diagnosis and is generally highest in the first few years, with the risk decreasing significantly as time from diagnosis lengthens.

### **COG LTFU Guidelines Methodology**

The methodology used in developing these guidelines has been described elsewhere.<sup>12</sup> Briefly, evidence for development of the *COG LTFU Guidelines* was collected by conducting a complete search of the medical literature for the previous 20 years via MEDLINE. A panel of experts in the late effects of childhood and adolescent cancer treatment then reviewed and scored the guidelines using a modified version of the National Comprehensive Cancer Network “Categories of Consensus” system. Task forces within COG monitor the literature on an ongoing basis and provide recommendations for guideline revision as new information becomes available. These task forces include general pediatricians and other primary care providers to incorporate a primary care perspective and facilitate effective dissemination of these guidelines into the “real-world” setting.

The *COG LTFU Guidelines* are updated on an every 5-year cycle to ensure that recommendations reflect currently available evidence published in peer-reviewed journals. Multidisciplinary system-based task forces (>160 COG members) are responsible for monitoring the late effects literature, performing systematic searches, summarizing and evaluating the evidence and presenting recommendations for guideline revisions to a multidisciplinary panel of late effects experts. Task force activities involve senior leaders who mentor early career physicians and other health care professionals in acquiring the leadership and methodologic skills to sustain guideline activities as a task force chair or member. A formal training program has been developed that includes a series of webinars (available live and recorded/archived on COG website) and one-on-one mentorship activities with *COG LTFU Guideline* task force chairs and leadership.

### **COG LTFU Guidelines Version 5.0**

The *COG LTFU Guidelines* is an online resource (available at [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org)). The *COG LTFU Guidelines* Version 5.0 features 165 sections of risk-based exposure-related clinical practice guidelines for screening and management of late effects resulting from treatment for pediatric malignancies related to any cancer experience, blood product transfusion, specific chemotherapeutic agents, radiation exposures to targeted tissues/organs, hematopoietic cell transplantation (as well as transplantation with chronic graft-versus-host disease), specific surgical procedures, and adult-onset cancer screening for standard and high-risk groups. Version 5.0 features key changes including guideline recommendations and content based on new research related to thresholds and risk factors for cardiovascular toxicity following treatment with anthracycline chemotherapy and chest radiation, prevalence data regarding pregnancy

associated cardiomyopathy, prevalence data related to occurrence of multiple hormonal deficiencies among survivors treated with cranial irradiation, and improved risk estimates about the contribution of radiation dose and treatment volume to risk of developing subsequent breast and colorectal carcinomas. In addition, previous radiation threshold doses linked to specific screening recommendations have been removed for all but 5 sections, because organ dosimetry is often not available to guide implementation of screening. This approach provides uniform screening recommendations for survivors with target organs receiving radiation exposure at any dose, which the expert panel agreed was reasonable considering that the screening recommendations focus primarily on history and physical examination, with only limited recommendation for laboratory or other diagnostic evaluations. Finally, the guideline format has been substantially simplified to provide clinical users with concise presentation of specific therapeutic exposures, potential late effects, screening recommendations, and relevant counseling and educational resources for the provider and survivors. Each guideline section features a brief summary of patient characteristics (eg, age, sex, pre-existing or comorbid conditions, behavioral, etc) that have been reported to modify the risk of specific late effects and cancer- and treatment-related factors that are important for consideration in the delivery of personalized survivor-focused care,<sup>13</sup> clarifying information about the potential late effect or surveillance recommendations, and representative references. The simplified guideline content is also featured in the Passport for Care, a web-based resource that facilitates the generation of personalized surveillance plan based on the *COG LTFU Guidelines* available at <https://cancersurvivor.passportforcare.org/>.<sup>14</sup>

This revised clinical report, “Long-term Follow-up Care for Childhood, Adolescent, and Young Adult Cancer Survivors,” has been updated to enhance awareness among health care providers about the content and scope of this comprehensive resource and offer time efficient methods of using the large amount of valuable information in the *COG LTFU Guidelines* to streamline the provision of care for these survivors. Table 1 provides a summary of selected treatment exposures and associated late effects by organ system as outlined in the *COG LTFU Guidelines*. Fig 1 provides an example of an exposure-based recommendation from the *COG LTFU Guidelines*. Full details about 155 cancer treatment-related potential biomedical and psychosocial late effects, surveillance recommendations, patient educational materials and other resources and websites pertinent to the specific health risks are available at [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org).

## CLINICAL APPLICATION OF *COG LTFU GUIDELINES*

Malignancies presenting in childhood, adolescence, and young adulthood encompass a spectrum of diverse histologic subtypes that have been managed with heterogeneous and evolving treatment approaches. Over the last 20 years, treatment protocols for localized and biologically favorable presentations of cancers have been modified substantially to reduce the risk of therapy-related complications. Conversely, therapy has been intensified for many advanced and biologically unfavorable cancers to optimize disease control and long-term survival. Thus, not all childhood, adolescent and young adult cancer survivors have similar risks of late treatment effects, including those with the same diagnosis. Importantly, cancer

treatment strategies continue to evolve as a result of discoveries in cancer biology and therapeutics as well as improved understanding about late effects.

### **Evaluating a Survivor's Risk of Late Effects**

In general, the risk of late effects is directly proportional to the intensity of therapy required to achieve and maintain disease control. Longer treatment with higher cumulative doses of chemotherapy and radiation, multimodal therapy, and relapse therapy increase the risk of late treatment effects. Specifically, the risk of late effects is related to the type and intensity of cancer therapy (eg, surgery, radiation therapy, chemotherapy, immunotherapy, and hematopoietic stem cell transplantation) and the patient's age at the time of treatment. Chemotherapy most often results in acute effects, some of which may persist and cause problems as the survivor ages. Many radiation-related effects on growth and development, organ function, and carcinogenesis may not manifest until many years after cancer treatment. The young child is especially at risk of delayed treatment toxicity affecting linear growth, skeletal maturation, intellectual function, sexual development, and organ function. It is important that health care professionals who provide care across a continuum of developmental periods also recognize that childhood cancer survivors face unique vulnerabilities related to their age at diagnosis and treatment. Table 2 provides examples of clinical and treatment factors that influence the risk of specific late effects after treatment for a common childhood (acute lymphoblastic leukemia) and adolescent-young adult (osteosarcoma) cancer. The diversity and potential interplay of factors contributing to cancer-related morbidity are further illustrated in the case presentations summarized in Table 3.

### **Using the *COG LTFU Guidelines* to Plan Survivorship Care**

Risk-based care involving a systematic plan for lifelong screening, surveillance, and prevention that incorporates risks on the basis of previous cancer, cancer therapy, genetic predispositions, lifestyle behaviors, and comorbid health conditions is recommended for all survivors.<sup>13</sup> Information critical to the coordination of risk-based care includes the date of cancer diagnosis, cancer histology, organs/tissues affected by cancer, and specific treatment modalities such as surgical procedures, chemotherapeutic agents, and radiation treatment fields and doses and history of bone marrow or stem cell transplant and blood product transfusion. Knowledge of cumulative chemotherapy dosages (eg, for anthracycline agents), or dose intensity of administration (eg, for methotrexate), also is important in estimating risk and screening frequency. This pertinent clinical information can be organized into a treatment summary that interfaces with the *COG LTFU Guidelines* to facilitate identification of potential late complications and recommended follow-up care (Fig 2). Because of the diversity and complexity of childhood, adolescent, and young adult cancer therapies, the treating oncology center represents the optimal resource for this treatment information. Furthermore, the need for ongoing, open lines of communication between the cancer center and the primary care provider is critical.

Coordination of risk-based care for childhood, adolescent and young adult cancer survivors requires a working knowledge about cancer-related health risks and appropriate screening evaluations, or access to a resource that contains this information. Often, late effects present

as a distinct clinical entity (eg, growth failure, heart failure, academic underachievement, etc) remote from cancer diagnosis and treatment. The primary care physician should consistently consider the contribution of cancer and its treatment to physical and emotional health conditions presenting in survivors, use the COG LTFU Guidelines to identify linkages of late effects and therapeutic exposures, and consult with local pediatric oncologists/late effects specialists to develop a strategy for further investigation. The *COG LTFU Guidelines* represent a comprehensive resource that can be utilized to plan cancer survivorship care as outlined in Fig 3. Individualized recommendations for long-term follow-up care of childhood, adolescent, and young adult cancer survivors can be customized from the *COG LTFU Guidelines* based on each patient's treatment history, age, and gender into a "survivorship care plan" that is ideally developed by, or in coordination with, the oncology subspecialist. The survivorship care plan is a living document that is meant to be reviewed by survivors and their health care providers at least yearly and updated as new health conditions emerge and health behaviors change over time. In addition, the *COG LTFU Guidelines* provide information to assist with risk stratification, allowing the health care provider to address specific treatment-related health risks that may be magnified in individual patients because of familial or genetic predisposition, sociodemographic factors, or maladaptive health behaviors. The patient education materials, known as "health links," that accompany the *COG LTFU Guidelines*, are specifically tailored to enhance health supervision and promotion in this population by providing simplified explanations of guideline-specific topics in lay language.<sup>15</sup> The *COG LTFU Guidelines*, associated patient education materials, and supplemental resources to enhance guideline application, including clinical summary templates, can be downloaded from [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org). A web-based platform that generates online therapeutic summaries with simultaneous output of patient-specific guidelines on the basis of exposure history, age, and gender is now accessible to institutions providing pediatric oncology follow-up care (<https://cancersurvivor.passportforcare.org/>).<sup>14</sup>

## DISCUSSION/RECOMMENDATIONS

Pediatricians and other primary care health care professionals are uniquely qualified to deliver ongoing health care to childhood, adolescent, and young adult cancer survivors, because they are already familiar with health maintenance and supervision for healthy populations and provide care for patients with complex chronic medical conditions. The concept of the "medical home" has been endorsed by the American Academy of Pediatrics as an effective model for coordinating the complex health care requirements of children with special needs, such as childhood cancer survivors, to provide care and preventive services that are accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective.<sup>16</sup> Within this framework, the pediatrician is able to view the cancer survivor in the context of the family and to assist not only the survivor but also the parents and siblings in adapting to the "new normal" of cancer survivorship. The focus of care for the childhood cancer survivor seen in a primary care practice is not the cancer from which the patient has now recovered but, rather, the actual and potential physical and psychosocial sequelae of cancer and its therapy and its impact on family functioning. Childhood, adolescent, and young adult cancer survivors are at a substantially

increased risk of morbidity and mortality when compared with the general population.<sup>5-10</sup> This updated clinical report delineates recommendations that aim to facilitate this vulnerable population's access to high-quality survivorship.

**Recommendation #1: Primary health care professionals should work collaboratively with the oncology subspecialist, to develop and implement the survivorship care plan and coordinate survivorship care.**

Ideally, the survivorship care plan is developed through a shared partnership that includes the primary care and oncology subspecialty providers, the survivor, and the family. Community providers can request a cancer treatment summary and survivorship care plan from the oncology center if this is not provided at the time that the survivor transitions back to the primary care setting. If a survivorship care plan is not provided by the primary oncology team, COG-affiliated subspecialty survivorship clinics can be consulted for assistance in coordinating survivorship care (<https://cogmembers.org/public/lateeffects/default.aspx>). In addition to the *COG LTFU Guideline* recommendations for late effects screening, the ideal survivorship care plan delineates provider(s) who will be coordinating the indicated screening evaluations and identifies provider(s) responsible for communicating and explaining the results to the patient and/or caregivers.

**Recommendation #2: The *COG LTFU Guidelines* should be used to guide the development of an individualized follow-up plan (survivorship care plan) based on the childhood, adolescent, or young adult survivor's specific cancer treatment and risk of late complications.**

Although late treatment effects can be anticipated in many cases based on therapeutic exposures, the risk to an individual patient is modified by multiple factors. The cancer patient may present with premorbid health conditions that influence tolerance to therapy and increase the risk of treatment-related toxicity. Cancer-related factors, including histology, tumor site, and tumor biology/response, often dictate treatment modality and intensity. Patient-related factors, such as age at diagnosis, and sex, may affect the risk of several treatment-related complications. Sociodemographic factors, such as household income, educational attainment, and socioeconomic status, often influence access to health insurance, remedial services, and appropriate risk-based health care. Organ senescence in aging survivors may accelerate presentation of age-related health conditions in survivors with subclinical organ injury or dysfunction resulting from cancer treatment. Genetic or familial characteristics may also enhance susceptibility to treatment-related complications. Problems experienced during and after treatment may further increase morbidity. Health behaviors, including tobacco and alcohol use, sun exposure, and dietary and exercise habits, may increase the risk of specific therapy-related complications. The *COG LTFU Guidelines* can assist the physician in maintaining a balance between overscreening (which could potentially cause undue fear of unlikely but remotely plausible complications as well as higher medical costs resulting from unnecessary screening) and underscreening (which could miss potentially life-threatening complications, thus resulting in lost opportunities for early intervention that could minimize morbidity).



**Recommendation #3: The survivorship care plan should include screening for potential adverse medical and psychosocial effects of the cancer experience.**

The follow-up evaluations of childhood adolescent and young adult cancer survivors should be individualized on the basis of their treatment history and may include screening for such potential complications as thyroid or cardiac dysfunction, second malignant neoplasms, neurocognitive difficulties, and many others.<sup>13</sup> In addition, providers should be mindful of the psychosocial late effects experienced by youth treated for cancer, particularly those that may affect educational and vocational progress, because provider advocacy and intervention can facilitate survivor access to remedial resources and programs in 504 and individual education plans and vocational training.<sup>17</sup> Likewise, as emotional health and family functioning may be affected by the cancer experience, proactive assessment of and referral to mental health services are important to optimize the quality of survivorship. Finally, personalized risk assessment would not be complete without consideration of socioeconomic and community factors that may affect access to survivorship resources and health care.

**Recommendation #4: The survivorship care plan should address the contribution of comorbid health conditions, familial/genetic factors, and health behaviors that affect the risk of chronic disease and provide interventions and resources to remediate and prevent late effects of cancer and promote healthy lifestyle behaviors.**

In addition to screening for late effects predisposed by previous therapeutic exposures, promotion of physical and mental health and well-being as part of a healthy lifestyle are important aspects of long-term follow-up care in this population. Numerous investigations have shown that survivors of childhood, adolescent, and young adult cancer have a high rate of chronic health conditions when followed long-term,<sup>6,8</sup> yet many lack awareness of their treatment-related health risks.<sup>18-20</sup> For this reason, it is recommended that health care professionals provide anticipatory guidance regarding health promotion and disease prevention aimed at minimizing the risk of future morbidity and mortality attributable to chronic physical and mental health conditions. For example, counseling survivors who are at risk of obesity, cardiovascular disease, and osteoporosis about the importance of adhering to healthful dietary guidelines, limiting sedentary lifestyle with or without screen time, and having regular physical activity is important. Education about cancer- and disease-prevention benefits offered through vaccination can also reduce health risks.

**Recommendation #5: Primary health care professionals should work collaboratively with the oncology subspecialist to educate survivors and their families about cancer treatment-related health risks, recommended health screening, and methods for risk reduction.**

Adolescent and young adult survivors need appropriate knowledge, skills, and opportunities to learn and make decisions about their own health maintenance needs, their potential physical and mental health risks, recommended health screening related to these risks, the impact of health behaviors on physical and mental health risks, and strategies to reduce health risks. Collaboration between the oncology and primary care teams can help to ensure that survivors' educational needs are addressed. Innovative electronic and mobile health platforms represent evolving technologies that can be leveraged to educate and empower

survivors preparing for health care transitions by promoting self-management of chronic health conditions and connecting them with survivorship communities and resources.<sup>21</sup> The *COG LTFU Guidelines* can be used as a resource to facilitate targeted education regarding cancer and treatment-related health risks and health promotion. The *COG LTFU Guideline Health Links* (available at [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org)) can be printed for distribution in the primary care office setting and are available for viewing by patients and their caregivers on the Internet.<sup>15</sup> In this process, it is important for health care professionals to be aware that some survivors, given their young age at diagnosis, may not remember their cancer diagnosis or the treatment that they received, or may not have been told about their cancer history.<sup>22-24</sup>

**Recommendation #6: Primary health care professionals should work collaboratively with the oncology subspecialist to prepare survivors and their families for health care transitions.**

Ensuring a smooth transition from pediatric to adult-oriented health care services poses additional challenges in the care of childhood cancer survivors as they age out of the pediatric health care system. Because adults treated for childhood cancer represent a rare population in primary care practices, practical and educational efforts of clinicians may be focused on more prevalent primary care issues. Consequently, family physicians, internists, practitioners trained in internal medicine and pediatrics (med-peds), and advanced practice providers who ultimately assume care of most adults treated for childhood cancer endorse low comfort levels and a desire for resources and guidance in managing survivors.<sup>25,26</sup> These data underscore the importance of communication between oncology and primary care providers in health care transition planning. Pretransition planning is a critical element in the successful transition from pediatric to adult-oriented health care for all adolescents and young adults with special health care needs, including cancer survivors. The medical home model provides a strong foundation for this planning.<sup>27</sup> The updated American Academy of Pediatrics clinical report “Supporting the Health Care Transition From Adolescence to Adulthood in the Medical Home” emphasizes the critical role of adult care clinicians in accepting and partnering with young adults to optimize health care transitions.<sup>28</sup> In addition, the report provides practical guidance on the key elements of transition planning and implementation for medically vulnerable populations. For childhood cancer survivors, a pretransition plan ideally outlines the roles of patient, family, subspecialty, and community health care providers in the ongoing care of the survivor to ensure a successful transition. Importantly, in this process providers should respect the evolving autonomy and privacy concerns of adolescents and young adults in health care discussions and decision making, particularly related to sexual and reproductive health that may be adversely affected by the cancer experience in some survivors.<sup>29,30</sup>

**Recommendation #7: Primary health care professionals should work collaboratively with the oncology subspecialist to educate survivors and their families about resources to facilitate their access to survivorship care.**

Laws that extend medical coverage into young adulthood can facilitate survivors’ access to timely, high-quality, and affordable survivorship care.<sup>31</sup> This is particularly relevant as survivors experience increased risk for multimorbidity as they age, and health conditions

often present at a younger age of onset compared with individuals who have not had cancer. For example, primary care providers may not be aware of the need for early initiation of breast cancer surveillance among young adult women treated with chest radiation for childhood cancer. Delineating this risk in the survivorship care plan and providing appropriate letters of medical necessity can facilitate awareness by providers and insurance coverage of recommended surveillance imaging.<sup>32</sup> Finally, considering research demonstrating that a substantial proportion of young adult survivors are uninsured or underinsured, transition planning should identify community resources to address medical needs, including emotional health and rehabilitation services. Payers should facilitate communication among providers in the design of their provider networks and by adequate payment for care coordination.<sup>33</sup>

## SUMMARY

Given the high incidence of late effects experienced by cancer survivors, individuals treated for cancer during childhood, adolescence, or young adulthood require long-term follow-up care from knowledgeable providers so their care is appropriately tailored to their specific treatment-related risk factors. Models of survivorship care vary substantially across clinical settings based on resource availability. Because multidisciplinary late effects clinics are not consistently accessible to or utilized by cancer survivors, pediatricians and other primary care providers represent critical participants in delivery of survivorship care.<sup>34,35</sup> The *COG LTFU Guidelines* provide a readily accessible resource to address knowledge deficits related to health risks associated with treatment for childhood, adolescent or young adult cancer. Availability of this resource is particularly important as the population of long-term survivors continues to increase as a result of the effectiveness of contemporary treatment approaches.

Ultimately, the goal of this clinical report from the American Academy of Pediatrics is to increase the awareness of general pediatricians and other primary health care professionals regarding the readily available resource of the *COG LTFU Guidelines* and the ability to consult with multidisciplinary long-term follow up clinics for childhood, adolescent, and young adult cancer survivors. These guidelines can, in turn, be used to develop a comprehensive yet individualized survivorship care plan for each cancer survivor who can be supported to work toward a planned transition to adult health care providers in primary and specialty care.

The survivorship care plan is a “road map” for primary health care professionals for providing risk-based, long-term follow-up care in the community setting. Ongoing communication between the cancer center and the primary care provider is the cornerstone for providing high-quality care to this vulnerable patient population.

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## **Appendix**

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## ABBREVIATIONS:

|                            |  |
|----------------------------|--|
| <b>COG</b>                 | Children's Oncology Group  |
| <b>COG LTFU Guidelines</b> | Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers |

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| RADIATION  |                        |   |  | POTENTIAL IMPACT TO LUNGS   |
|--|------------------------|---|--|---|
| Sec #  | Therapeutic Exposure   | Potential Late Effects  | Periodic Evaluation  | Health Counseling/<br>Further Considerations  |
| 74   | Chest<br>Axilla<br>TBI | <b>Pulmonary toxicity</b><br>Pulmonary fibrosis<br>Interstitial pneumonitis<br>Restrictive lung disease<br>Obstructive lung disease | <b>HISTORY</b><br>Cough<br>Wheezing<br>Shortness of breath<br>Dyspnea on exertion<br>Yearly<br><b>PHYSICAL</b><br>Pulmonary exam<br>Yearly<br><b>SCREENING</b><br><b>PFTs (including DLCO and spirometry)</b><br>Baseline at entry into long-term follow-up, repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction | <b>HEALTH LINKS</b><br>Pulmonary Health<br><b>RESOURCES</b><br>www.smokefree.gov<br><b>COUNSELING</b><br>Tobacco avoidance/smoking cessation/environmental tobacco smoke.<br><b>POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION</b><br>Repeat PFTs prior to general anesthesia.<br>Influenza and Pneumococcal vaccinations.<br>Pulmonary consultation for patients with symptomatic pulmonary dysfunction.<br>Pulmonary consultation for survivors who desire to SCUBA dive (due to potential undiagnosed pulmonary toxicities, and limited data to guide safe diving recommendations for individuals treated with pulmonary toxic therapy).<br><br><b>SYSTEM = Pulmonary</b><br><b>SCORE = 1</b> |
| <b>Additional Information</b>  |                        |   |  |   |
| Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.   |                        |   |  |   |
| <ul style="list-style-type: none"> <li>- Patient factors: Younger age at irradiation</li> <li>- Cancer/Treatment factors: Radiation dose &gt;10 Gy, especially radiation dose ≥15 Gy, TBI ≥6 Gy in single fraction, TBI ≥12 Gy fractionated, chest radiation combined with TBI, radiation combined with bleomycin, busulfan, carmustine (BCNU), or lomustine (CCNU), radiomimetic chemotherapy (e.g., doxorubicin, dacarbazine)</li> <li>- Pre-morbid/Co-morbid medical conditions: Atopic history</li> <li>- Health behaviors: Smoking, inhaled illicit drug use</li> </ul>   |                        |   |  |   |
| <b>References</b>  |                        |   |  |   |
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**Fig 1. Example of an exposure-based recommendation from the COG LTFU Guidelines** (From the *Children’s Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers, Version 5.0, October 2018*, used with permission).



### Summary of Cancer Treatment (Abbreviated)

| Demographics  |  |  |
|---|--|--|
| Name  | Sex <input type="checkbox"/> M <input type="checkbox"/> F                | Date of Birth  |
| Cancer Diagnosis  |  |  |
| Diagnosis   | Date of Diagnosis  | Date Therapy Completed   |
| Chemotherapy <input type="checkbox"/> Yes <input type="checkbox"/> No <i>If yes, provide information below</i>  |  |  |
| Drug Name   | Additional Information <sup>†</sup>                                      |  |
|   |  |  |
|   |  |  |
|   |  |  |
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|   |  |  |
|   |  |  |
|   |  |  |
|   |  |  |
|   |  |  |
| <sup>†</sup> <b>Anthracyclines:</b> Include cumulative dose in mg/m <sup>2</sup> (see section 33 of Guidelines for isotoxic dose conversion);<br><b>Carboplatin:</b> Indicate if dose was myeloablative<br><b>Methotrexate and Cytarabine:</b> Indicate route of administration (i.e., IV, IM, SQ, PO, IT, ID);<br><b>IV Methotrexate and Cytarabine:</b> Indicate if "high dose" (any single dose ≥ 1000 mg/m <sup>2</sup> ) or "standard dose" (all single doses < 1000 mg/m <sup>2</sup> )<br><b>Note:</b> Cumulative doses, if known, should be recorded for all agents, particularly for alkylators and bleomycin. |  |  |
| Radiation <input type="checkbox"/> Yes <input type="checkbox"/> No <i>If yes, provide information below</i>   |  |  |
| Site/Field  | Total Dose* (including boost) (Gy)**                                     |  |
|   |  |  |
| *For head/brain, neck, chest, abdomen, spine (whole, cervical, thoracic) radiation and TBI, include total doses (including boost dose, if given)<br>**To convert cGy or rads to Gy, divide dose by 100 (example: 2400 cGy = 2400 rads = 24 Gy)  |  |  |
| Hematopoietic Cell Transplant <input type="checkbox"/> Yes <input type="checkbox"/> No <i>If yes, provide information below</i>   |  |  |
| Transplant Type   | Autologous <input type="checkbox"/> Yes <input type="checkbox"/> No      | Allogeneic <input type="checkbox"/> Yes <input type="checkbox"/> No        |
| Chronic Graft-Versus-Host Disease (cGVHD)   | Ever diagnosed? <input type="checkbox"/> Yes <input type="checkbox"/> No | Currently active? <input type="checkbox"/> Yes <input type="checkbox"/> No |
| Surgery <input type="checkbox"/> Yes <input type="checkbox"/> No <i>If yes, provide information below</i>   |  |  |
| Procedure   | Site (if applicable)   | Laterality (if applicable)   |
|   |  |  |
|   |  |  |
|   |  |  |
| Other Therapeutic Modalities <input type="checkbox"/> Yes <input type="checkbox"/> No <i>If yes, provide information below</i>  |  |  |
| Did the patient receive radiiodine therapy (I-131 thyroid ablation)? <input type="checkbox"/> Yes <input type="checkbox"/> No   |  |  |
| Did the patient receive systemic MIBG (in therapeutic doses)? <input type="checkbox"/> Yes <input type="checkbox"/> No  |  |  |
| Summary prepared by:  |  | Date prepared:   |

COG Summary of Cancer Treatment (Abbreviated Version)

Version 5.0 – October 2018

**Fig 2. Sample template for cancer treatment summary containing essential data elements necessary for generating long-term follow-up guidelines**  
 (From the *Children’s Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers*, Version 5.0, October 2018, used with permission).

- Request a cancer treatment summary and survivorship care plan from the survivors' oncology team if possible.
- Request medical records to organize a cancer treatment summary and survivorship care plan if a care plan is not provided by the oncology team.
- Use the summary of cancer treatment template at [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org) or <https://cancersurvivor.passportforcare.org/> to develop the survivorship care plan.
- Identify patient (eg, age at diagnosis, sex), cancer (eg, histology, involved organs/tissues), and treatment (surgery, chemotherapy, radiotherapy, hematopoietic cell transplant) details that may influence the risk of late effects.
- Consult the *COG LTFU Guidelines* at [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org) to determine health risks associated with specific exposures and recommended health screening. Use the bookmark feature to identify the guideline sections pertinent to your survivor.
- Consider patient- and cancer-treatment related factors, pre-existing/comorbid health conditions, and health behaviors, as appropriate, that may increase risk listed under "Additional Information" of each guideline section.
- Use the *COG LTFU Guidelines Health Links* and other educational resources listed under "Further Considerations."
- Address psychosocial factors that can affect access to health care and resources to prevent or remediate late effects.
- Contact an established long-term follow-up childhood cancer survivor program for assistance in managing complex survivorship-related needs and identifying survivorship resources. COG-affiliated subspecialty survivorship clinics are available at <https://cogmembers.org/public/lateeffects/default.aspx>.

**Fig 3. How to use the COG LTFU Guidelines to plan cancer survivorship care**

**Table 1.** Potential Late Effects of Selected Therapeutic Interventions for Childhood, Adolescent and Young Adult Cancer by Organ

| Organ                               | Therapeutic Exposures  |  |                                     | Potential Late Effect  |
|-------------------------------------|--|--|-------------------------------------|--|
|                                     | Chemotherapy   | Radiation Therapy Field(s)                         | Surgery                             |  |
| Any organ/tissue                    |  | All fields   |                                     | Subsequent neoplasms (skin, breast, thyroid, brain, colon, bone, soft tissues, etc)  |
| Bones                               | Corticosteroids<br>Methotrexate  | --   | --                                  | Osteopenia/osteoporosis<br>Osteonecrosis   |
| Bones/soft tissues                  | --   | All fields   | --                                  | Reduced/uneven growth<br>Reduced function/mobility<br>Hypoplasia, fibrosis<br>Radiation-induced fracture<br>Scoliosis/kyphosis (trunk fields only)                   |
| Bones/soft tissues                  | --   | --   | Amputation<br>Limb sparing          | Reduced/uneven growth<br>Reduced function/mobility<br>Chronic pain   |
| Bowel                               | --   | Abdomen<br>Pelvis<br>Spine (lumbar, sacral, whole) | Laparotomy<br>Pelvic/spinal surgery | Chronic enterocolitis<br>GI tract strictures<br>Adhesions/obstruction<br>Fecal incontinence  |
| Bladder                             | Cyclophosphamide<br>Ifosfamide   | Pelvic<br>Spine (sacral, whole)                    | Spinal surgery<br>Cystectomy        | Hemorrhagic cystitis<br>Bladder fibrosis<br>Dysfunctional voiding<br>Neurogenic bladder  |
| Brain (cognitive function)          | Methotrexate (intrathecal administration or IV doses 1000 mg/m <sup>2</sup> )<br>Cytarabine (IV doses 1000 mg/m <sup>2</sup> ) | Head/Brain<br>Total body                           | Neurosurgery                        | Neurocognitive deficits (executive function, attention, memory, processing speed, visual motor integration)<br>Learning deficits<br>Diminished intelligence quotient |
| Brain (motor and sensory function)  | Methotrexate, cytarabine (intrathecal administration or IV doses 1000 mg/m <sup>2</sup> )                                      | Head/Brain   | Neurosurgery                        | Cranial nerve dysfunction<br>Motor and sensory deficits including paralysis<br>Cerebellar dysfunction<br>Seizures  |
| Brain (hypothalamic-pituitary axis) | --   | Head/Brain<br>Total body                           | Neurosurgery                        | Growth hormone deficiency<br>Precocious puberty (altered gonadotropin secretion)<br>Gonadotropin insufficiency<br>Central adrenal insufficiency (XRT 30 Gy)          |
| Brain (vascular)                    | --   | Head/Brain   | Neurosurgery                        | Cerebrovascular complications (stroke, moya moyo, occlusive cerebral vasculopathy)   |
| Breast                              | --   | Chest<br>Axilla<br>Total body                      | --                                  | Breast tissue hypoplasia<br>Breast cancer  |

| Organ               | Therapeutic Exposures   |   |                                  | Potential Late Effect  |
|---------------------|---|---|----------------------------------|--|
|                     | Chemotherapy  | Radiation Therapy Field(s)                                    | Surgery                          |  |
| Ear                 | Cisplatin<br>Carboplatin (in myeloablative doses only)  | Head/Brain  | --                               | Sensorineural hearing loss (XRT doses > 30 Gy)<br>Conductive hearing loss (XRT only)<br>Eustachian tube dysfunction (XRT only)   |
| Esophagus           |   | Neck<br>Chest<br>Abdomen<br>Spine (cervical, thoracic, whole) |                                  | Esophageal stricture   |
| Eye                 | Busulfan<br>Corticosteroids   | Head/Brain<br>Total body                                      | Neurosurgery                     | Cataracts<br>Retinopathy (XRT only)<br>Ocular nerve palsy (neurosurgery only)  |
| Heart               | Anthracycline agents (eg, doxorubicin, daunorubicin)  | Chest<br>Abdomen<br>Spine (thoracic, whole)<br>Total body     | --                               | Cardiomyopathy<br>Congestive heart failure<br>Arrhythmia<br>Subclinical left ventricular dysfunction<br>XRT only: <ul style="list-style-type: none"> <li>• Valvular disease</li> <li>• Atherosclerotic heart disease</li> <li>• Myocardial infarction</li> <li>• Pericarditis, pericardial fibrosis</li> </ul> |
| Kidney              | Cisplatin<br>Carboplatin<br>Ifosfamide<br>Methotrexate  | Abdomen<br>Total body   | Nephrectomy                      | Glomerular toxicity<br>Tubular dysfunction<br>Renal insufficiency<br>Hypertension  |
| Liver/biliary tract | Antimetabolites (mercaptopurine, thioguanine, methotrexate)   | Abdomen   | --                               | Hepatic dysfunction<br>Veno-occlusive disease<br>Hepatic fibrosis, cirrhosis<br>Cholelithiasis   |
| Lungs               | Bleomycin<br>Busulfan<br>Carmustine<br>Lomustine  | Chest<br>Axilla<br>Total body                                 | Pulmonary resection<br>Lobectomy | Pulmonary fibrosis<br>Interstitial pneumonitis<br>Restrictive/obstructive lung disease<br>Pulmonary dysfunction  |
| Nerves (peripheral) | Plant alkaloids (vincristine, vinblastine)<br>Cisplatin, carboplatin  | --  | Spinal surgery                   | Peripheral sensory or motor neuropathy   |
| Ovary               | Alkylating agents (eg, busulfan, carmustine, lomustine, cyclophosphamide, mechlorethamine, melphalan, procarbazine) | Pelvis<br>Spine (sacral, whole)<br>Total body                 | Oophorectomy                     | Ovarian hormone insufficiency<br>Delayed/arrested puberty<br>Premature menopause<br>Diminished ovarian reserve<br>Infertility  |

| Organ   | Therapeutic Exposures   |   |                                      | Potential Late Effect  |
|---------|---|---|--------------------------------------|--|
|         | Chemotherapy  | Radiation Therapy Field(s)                                  | Surgery                              |  |
| Skin    | --  | All fields  | --                                   | Uterine vascular insufficiency (XRT only)<br>Vaginal fibrosis/stenosis (XRT only)<br><br>Permanent alopecia<br>Altered skin pigmentation<br>Telangiectasias<br>Fibrosis<br>Dysplastic nevi |
| Spleen  |   | Abdomen (doses 40 Gy)                                       | Splenectomy                          | Life-threatening infection related to functional or anatomic asplenia <sup>a</sup>   |
| Teeth   | Any chemotherapy before development of secondary dentition  | Head/Brain<br>Neck<br>Spine (cervical, whole)<br>Total body | --                                   | Dental maldevelopment (tooth/root agenesis, microdontia, enamel dysplasia)<br>Periodontal disease<br>Dental caries<br>Osteoradionecrosis (XRT doses 40 Gy)                                 |
| Testes  | Alkylating agents (eg, busulfan, carmustine, lomustine, cyclophosphamide, mechlorethamine, melphalan, procarbazine) | Testes<br>Total body  | Pelvic/spinal surgery<br>Orchiectomy | Testosterone insufficiency<br>Delayed/arrested puberty<br>Impaired spermatogenesis<br>Infertility<br>Erectile/ejaculatory dysfunction  |
| Thyroid |   | Head/Brain<br>Neck<br>Spine (cervical, whole)<br>Total body | Thyroidectomy                        | Hypothyroidism<br>Hyperthyroidism<br>Thyroid nodules (XRT only)  |

Gy indicates Gray; IV, intravenous; XRT, radiation therapy.

Note: This table briefly summarizes potential late effects for selected therapeutic exposures only; the complete set of Long-Term Follow-Up Guidelines from the Children's Oncology Group, including screening recommendations, is available at [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org). In addition to organ/tissue-specific late effects, any cancer experience may increase the risk of adverse psychosocial and quality-of-life outcomes summarized at [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org) (sections 1-6).

<sup>a</sup>Functional asplenia can also occur as a consequence of active chronic graft-versus-host disease following hematopoietic stem cell transplant

**Table 2.** Clinical and Treatment Factors Influencing Risk of Late Effects after Childhood, Adolescent and Young Adult Cancer

| Factor                                | Reason   | Example(s)  |
|---------------------------------------|--|---|
| Age at diagnosis of cancer            | Age at diagnosis influences vulnerability to specific cancer treatment-related complications.  | Young children experience a higher risk of neurocognitive deficits following cranial irradiation compared to adolescents. <sup>36</sup><br>Young girls, compared with older adolescents, are less vulnerable to alkylating agent-induced ovarian insufficiency because of their larger primordial follicular pool. <sup>37</sup>  |
| Sex                                   | The risk of some cancer treatment-related toxicities varies by sex.  | Boys are more sensitive to gonadal injury following alkylating agents compared with girls. <sup>38</sup><br>Breast cancer risk in women treated with chest radiation is comparable to BRCA mutation carriers and warrants early initiation of breast cancer surveillance. <sup>39</sup>   |
| Tissues and organs involved by cancer | Malignant infiltration of normal tissues may result in permanent deficits.   | Survivors of central nervous system tumors may have long-term neurologic, neurosensory, or neuroendocrine late effects related to tumor location. <sup>40</sup><br>Survivors of retroperitoneal tumors (eg, Wilms tumor, neuroblastoma) experience increase risk of scoliosis. <sup>41</sup>  |
| Surgery                               | Specific surgical procedures may be associated with increased risks for chronic symptoms or health conditions.   | Sarcoma survivors treated with limb-sparing surgeries may have chronic pain or performance restrictions. <sup>42</sup><br>Survivors of Wilms tumor have an increased risk of hypertension after nephrectomy. <sup>43</sup>  |
| Chemotherapeutic agents               | Chemotherapeutic agents have unique organ/tissue toxicity profiles, many of which are dose-related. Knowledge of specific chemotherapy agents received is needed to determine type and magnitude of late effects risk. | Anthracyclines are associated with increased risk of cardiomyopathy. <sup>44</sup><br>Cisplatin increases the risk of hearing loss and renal dysfunction. <sup>45</sup><br>Alkylating agents increase the risk of gonadal injury and infertility. <sup>37</sup>   |
| Radiation therapy                     | The potential for radiation injury to normal tissues is directly related to the organs and tissues in the radiation treatment field and dose delivered.  | Hypothalamic-pituitary axis (HPA) dysfunction is common after cranial radiation. HPA systems affected show relationships to dose with growth hormone deficiency presenting at much lower dose exposure compared to gonadotropin deficiency. <sup>46</sup>   |
| Hematopoietic cell transplant         | In addition to risks associated with chemotherapy and radiation, survivors may experience health risks associated with immune system alterations following hematopoietic cell transplantation.                         | Survivors who are transplant recipients have higher risks of subsequent malignancies involving epithelial and mucosal tissues. <sup>47</sup>  |
| Pre-existing/comorbid conditions      | Common comorbid conditions can exacerbate cancer treatment-related toxicity. Management of ongoing comorbidities should be addressed during follow-up visits.  | Hypertension potentiates anthracycline-associated risk for heart failure. <sup>48</sup><br>Diabetes and hypertension potentiate radiation-associated risk for stroke. <sup>49</sup>   |
| Health behaviors and lifestyle        | Health behaviors can mitigate or magnify risk of cancer treatment-related toxicities.  | Adherence to recommended levels of moderate to vigorous physical activity reduces risk of major cardiac events and mortality in childhood cancer survivors. <sup>50,51</sup><br>Smoking increases the risk of pulmonary function deficits and subsequent malignancies. <sup>52</sup>  |
| Psychosocial                          | Sociodemographic factors may affect survivors' access to health care and resources to prevent or remediate late effects. Pre-morbid and co-morbid emotional health conditions are associated with adverse outcomes.    | Survivors with (of those from households with) lower income and educational levels are more vulnerable to impaired health status and financial toxicity. <sup>53</sup><br>Survivors experiencing psychological distress are more likely to participate in health risking behaviors (eg, tobacco, alcohol, and substance use). <sup>54,55</sup>  |
| Genetics                              | Cancer predisposition genes as well as common genetic variants (single nucleotide polymorphisms) are associated with increased risk of subsequent neoplasms and other treatment-related organ dysfunction.             | Survivors of retinoblastoma with RB1 mutation (all bilateral/familial cases) have an increased risk of subsequent malignant neoplasms, especially osteosarcoma. <sup>56</sup><br>Several genetic variations that may modify risk for cardiomyopathy in anthracycline-exposed survivors (eg, <i>SLC28A3</i> , <i>UGT1A6</i> , <i>RARG</i> , <i>CELE4</i> , <i>HAS5</i> ) have been identified. <sup>57</sup> |



Examples of 2 Survivors: Factors Contributing to Cancer-Related Morbidity After a Childhood and Adolescent-Young Adult Cancer<sup>a</sup>

Table 3.

| Factor                 | Example 1. Leukemia  | Example 2. Solid Tumor  |
|------------------------|--|---|
| Patient                | 3-year-old male  | 16-year-old female  |
| Tumor                  | Acute lymphoblastic leukemia, B lineage, average risk, without CNS involvement   | Embryonal rhabdomyosarcoma of the chest wall, stage II  |
| Treatment              | Antimetabolites (PO, IV, intrathecal)<br>Asparaginase<br>Corticosteroids<br>Cyclophosphamide (moderate dose)<br>Doxorubicin (low dose)<br>Vincristine  | Dactinomycin<br>Vincristine<br>Chest radiation (36 Gy)  |
| Potential late effects | Peripheral neuropathy<br>Osteopenia/osteoporosis<br>Osteonecrosis (rare for this age)<br>Cataracts (rare)<br>Hepatic dysfunction (very rare)<br>Renal insufficiency (very rare)<br>Neurocognitive deficits<br>Leukoencephalopathy<br>Hemorrhagic cystitis, bladder malignancy (very rare)<br>Secondary myelodysplasia or myeloid leukemia (very rare)<br>Gonadal dysfunction (rare)<br>Cardiomyopathy, congestive heart failure, arrhythmia (very rare)<br>Dental maldevelopment, periodontal disease, excessive dental caries | Peripheral neuropathy<br>Subclavian artery disease<br>Cardiac complications (cardiomyopathy, congestive heart failure, arrhythmia, subclinical left ventricular dysfunction, valvular disease, atherosclerotic heart disease, myocardial infarction, pericarditis, pericardial fibrosis)<br>Pulmonary complications (fibrosis, interstitial pneumonitis, restrictive/obstructive lung disease)<br>Esophageal stricture<br>Breast tissue hypoplasia<br>Breast cancer<br>Scoliosis/kyphosis<br>Shortened trunk height<br>Secondary benign or malignant neoplasms in radiation field |
| Genetics/familial      | Diabetes mellitus, type 2  | Hypertension<br>Early coronary artery disease   |
| Comorbid conditions    | Obesity<br>Anxiety   | Hypertension<br>Depression  |
| Health behaviors       | Sedentary lifestyle  | Smoker  |
| Aging                  | Reduced bone mineral density   | Cardiomyopathy  |

CNS indicates central nervous system; IV, intravenous; Gy, Gray; PO, oral.

<sup>a</sup>Recognition of dose-related toxicities has resulted in modification of therapies have substantially reduced risk of some late effects.