Accelerated Aging among Cancer Survivors: From Pediatrics to Geriatrics

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OVERVIEW

There are almost 14-million cancer survivors in the United States and the population is growing. Almost two-thirds of these survivors are age 65 or older. Given this, it is imperative to understand the impact of cancer and its therapies on the aging process. Childhood cancer survivors, diagnosed with cancer at age 21 or younger, particularly females, have rates of frailty similar to rates in older adults. This phenomenon appears to start early, suggesting an aging phenotype. Frailty among childhood cancer survivors increases risk for chronic disease and mortality. Adults diagnosed with cancer are faced with the effects of cancer and its therapies compounded by the issues of multiple morbidities that occur with the typical aging process. Intervention studies to date have focused on smoking cessation, diet, and exercise, as well as improving rates of late effects surveillance in childhood cancer survivors. No intervention studies have specifically addressed the issue of frailty or multiple morbidities in cancer survivors. Concerted efforts must continue to create and disseminate survivorship care plans to all cancer survivors.

It is currently estimated that there are over 13.7 million cancer survivors in the United States. The National Cancer Institute defines cancer survivors from the time of diagnosis until time of death. This population is steadily increasing in size[1] as a result of improvements in treatment as well as early detection. Furthermore, the general population is living longer and cancer rates tend to increase with age. It is estimated that two-thirds of all cancer survivors will be aged 65 or older by 2020.[2] Research in survivors of both pediatric and adult cancer has shown that success in the cure of cancer has come with a cost. Cancer and its therapies are associated with second malignancies and late effects that can affect any organ system. Given that older survivors are more likely to have multiple chronic health problems than younger survivors, it is imperative to understand the influence of cancer, its treatments, and associated late effects on the aging process. This understanding will enable health care providers to deliver appropriate risk-based care and interventions to minimize morbidities and maximize quality of life in this growing high-risk population.

CHILDHOOD CANCER SURVIVORS, CHRONIC DISEASE, AND AGING

Most large cohorts of childhood cancer survivors, such as the North American Childhood Cancer Survivor Study (CCSS), define survivors diagnosed at age 21 years or younger with a cancer as survivors if they are alive 5 years after initial diagnosis. The proportion of children diagnosed with cancer who survive 5 years after their original cancer diagnosis has improved from 57.9% in 1975 to over 83.1% in 2009.[3] There are nearly 380,000 survivors of childhood cancer living in the United States today.[3] Over 270,000 of these individuals are younger than age 40, with years of potential to actively and significantly contribute to family life, their communities, and society.[3] Unfortunately, treatment for childhood cancer, although curative, does not come without risk of late effects (Table 1). Surgical intervention, therapeutic radiation, and administration of chemotherapy do not always spare normal tissue, in some cases leaving the young survivor with less than optimal organ system structure and function.[4-6] Although most young adult cancer survivors do not have clinically significant chronic disease, some experience symptoms that interfere with or subtly limit their abilities to participate fully in life roles at home, at work, and in the community or during recreational activities. These symptoms may include fatigue,[7,8] shortness of breath,[9] or an inability to fully engage in activities that require exertion.[10] Such symptoms are all markers of reduced physiologic capacity, and may indicate an increased risk for developing early onset of chronic diseases, hospitalization, and death.

Accumulating evidence indicates that impairment of physiologic health early in life[11] may make childhood cancer survivors more vulnerable than the rest of the population to conditions and diseases often associated with aging, such as heart disease,[12,13] diminished pulmonary function,[14] and sec-

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TABLE 1. Late Effects Of Cancer And Its Treatment: "Aging Mimicry"?

CARDIOVASCULAR	Cardiomyopathy	**ENDOCRINE**	Osteoporosis
	Atherosclerotic CVD		Obesity, Metabolic syndrome
	LV dysfunction-CHF		Hypothyroidsm
	Arrythmias		Premature menopause
	Pericarditis		
	Valve dysfunction		Increased Infections
		IMMUNE SYSTEM	Asplenia
PULMONARY	Interstitial Pneumonitis		
	Pulmonary Fibrosis	**HEMATOLOGIC**	Myelodysplasia
	Restrictive lung disease		
	Obstructive lung disease		Peripheral Neuropathy
		NEUROLOGIC	Leukoencephalopathy
RENAL/GENITOURINARY	Glomerular toxicity		Stroke
	Tubular dysfunction		Cerebellar dysfunction
	Erectile dysfunction		Cognitive dysfunction
	Dyspareunia		
		HEPATIC	Decreased hepatic function
	Hearing loss		Intestinal obstruction
SENSORY	Tinnitus		
	Decreased vision	**GENERAL**	Fatigue
	Cataracts		

Abbreviations: CVD, cardiovascular disease; LV, left ventricle; CHF, congestive heart failure.

ond cancers.[15-17] In addition, recently presented[18] and published[19,20] data indicate that young adult survivors of childhood cancer have reduced physiologic reserve, such that some young survivors in their 20s and 30s are similar to individuals in their sixth and seventh decades of life in terms of muscle strength and power, mobility, and endurance. In the elderly, these impairments are associated with frailty, a phenotype predictive of chronic disease onset, disability, and mortality.[21] Supporting this contention is the fact that over two-thirds of childhood cancer survivors will have at least one chronic condition 30 years from diagnosis and over a quarter will have a condition that is life threatening or disabling,[6,22] rates 3.3 and 8.2 times higher than those of their peers. Childhood cancer survivors are more likely to report problems with function and activity than their siblings,[23] and experience declines in health status and physical function at an accelerated trajectory as they age.[24] In addition, mortality rates among adult survivors of childhood cancer are 8 times higher than expected when compared to the general population.[25,26]

KEY POINTS

- **Childhood cancer survivors, particularly women, have rates of frailty similar to rates in older adults. This phenomenon appears to start early, suggesting an aging phenotype.**
- **Frailty among childhood cancer survivors increases risk for chronic disease and mortality.**
- **60% of cancer survivors in the United States are over age 65 and are facing the issues of multiple morbidities from the interplay of the aging process and effects of cancer therapy.**
- **Intervention studies to date have focused on smoking cessation, diet, and exercise, as well as improving rates of late effects surveillance in childhood cancer survivors.**
- **No intervention studies have specifically addressed the issue of frailty in cancer survivors.**

Frailty

Frailty is a state of reduced physiologic reserve that increases susceptibility to chronic disease and disability.[27] In an aging adult population, intrinsic or attained physiologic capacity declines over time, beginning with subtle losses of neuromuscular control, deteriorating mechanical performance, and alterations in normal energy metabolism. The additive effects of typical poor lifestyle choices confer progressive low-grade physiologic loss. This trajectory of loss may be accelerated by acute insults (illness, injuries, major life events) that result in permanent organ system damage, often compounded by acute inactivity and bed rest. Frailty results when an individual does not have sufficient reserve to overcome the barriers that prevent organ system recovery after periods of rapid physiologic loss (Fig. 1).[21,28] This decline in physiologic reserve is subtle and clinically silent, recognizable only when specific functional, behavioral, or biologic measures are undertaken.[29] As such, frailty is a useful construct, distinguishable from symptomatic chronic disease and disability.

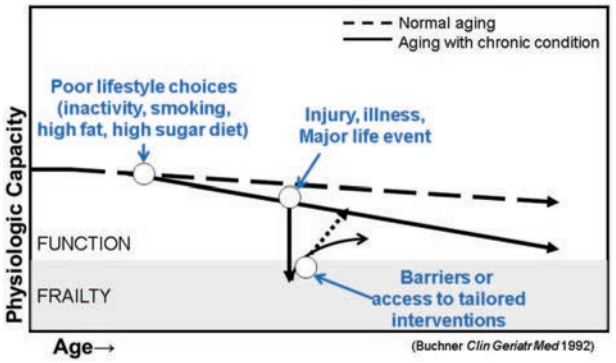

FIG 1. Frailty.

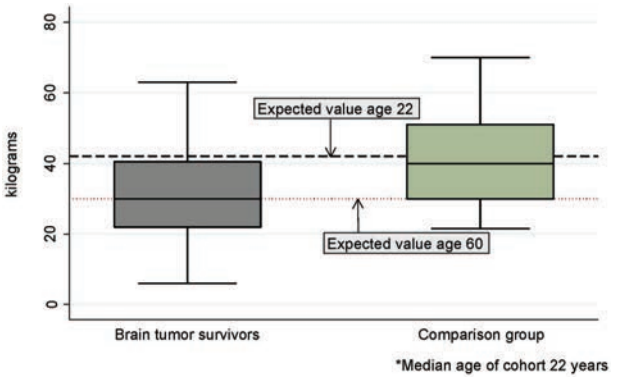

FIG 2. Handgrip strength among brain tumor survivors and an age- and sex-matched comparison group.

Defining and recognizing physiologic capacity in any vulnerable population is useful and important, not only as a predictor of future adverse health outcomes, but also as an indicator for early intervention.[29] To some extent, changing the slope of the line representing age- or disease-related physiologic decline is possible through interventions targeted at key health behaviors, which may in turn prevent early onset of frailty. Frailty prevention requires a system that promotes cost-effective medical screening for serious diseases amenable to early detection and treatment, and a mechanism to encourage individuals to adopt a lifestyle that maintains neuromuscular control, promotes muscle strength, and optimizes energy metabolism.[30]

Frailty in Childhood Cancer Survivors

Recently published and presented evidence supports the hypothesis that adult survivors of childhood cancer have diminished physiologic reserve, and that frailty among childhood cancer survivors occurs decades earlier than expected. In one investigation, physical performance among survivors of childhood brain tumors was compared to that of age-, gender-, race-, and zip code-matched members of the general population.[20] Results of this study indicated that among 78 survivors of childhood brain tumors (median age 22 years; range, 18 to 58) cardiopulmonary fitness and muscle strength values (in the unaffected extremity in cases of hemiplegia) were not only lower than those of the comparison group, but also very close to fitness levels and strength values observed among persons in their seventh decade of life (Fig. 2).[20] Another investigation evaluated neuromuscular impairments in survivors of childhood acute lymphoblastic leukemia (ALL) and reported that, among 415 survivors of childhood ALL with a median age of 35 years (range, 21 to 52) who were 10 or more years from diagnosis, 6-minute walk distances and knee extension strength values were more than 1.3 standard deviations less than expected in 46.5% and 30.1% of patients respectively, compared to age- and sex-matched normative data. The average distance walked in 6 minutes among these ALL survivors was similar to predicted distances for individuals aged 50 to 60 (Fig. 3).[19] Data presented at the 2011 American Society for Clinical Oncology (ASCO) annual meeting demonstrated that muscle weakness and poor endurance were prevalent among adult survivors of Hodgkin lymphoma (HL) who were at least 10 years from their original diagnosis. Those with measured performance in the lowest 10th percentile of age- and sex-predicted norms for strength and endurance were classified as having severe limitations. Among 188 HL survivors with median age 40 years (range 26 to 61) and median time since diagnosis of 26 years (range, 11 to 45), 22.3% had severe ankle weakness, 21.8% had severe quadriceps weakness, and 31.9% performed in the severely impaired range on the 6-minute walk test.[18]

These results extend to a large cohort of adult survivors of various childhood cancer diagnoses. In an investigation designed to examine the frailty phenotype, we applied the Fried Model to 1,922 members of the St. Jude Lifetime Cohort Study.[31,32] Among these 10-year or more survivors of childhood cancer (50.3% male, median age 32 years [range 18 to 59], age at diagnosis 6 years [range 0 to 21]), physical function was evaluated and prefrailty and frailty were respectively defined as meeting at least two and three of the following criteria: sarcopenia, decreased muscle strength, poor endurance, slow walking speed, and low levels of activity. Nearly one-third (31.5%) of women and 12.9% of men met prefrailty criteria and 13.1% of women and 2.7% of men met frailty criteria. Frailty was not present among members of a healthy

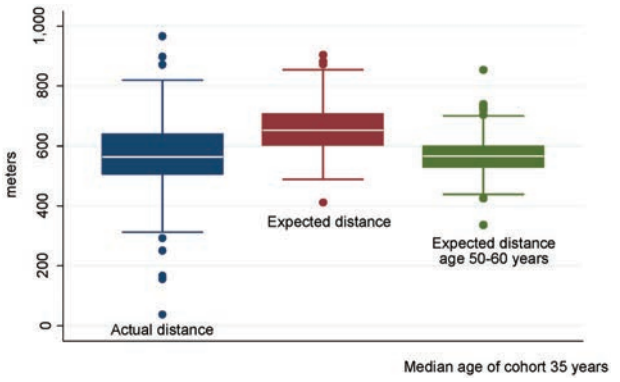

FIG 3. Six-minute walk distance among ALL survivors.

comparison group who received the same testing. Among survivors, frailty increased with age among females (7.1%, 12.5%, and 24.9% of individuals aged 18 to 29, 30 to 39, and 40 to 59 years respectively). The combined prevalence of pre-frailty/frailty was highest among survivors of central nervous system tumors (41.2%), soft tissue sarcoma (39.4%), and other solid tumors (38.7%). Those exposed to cranial radiation were more likely to have two or more components of the frailty phenotype when compared to those who were not exposed to cranial radiation (52.8% vs. 40.1% for females; 19.9% vs. 13.1% for males). In this young adult cohort of survivors frailty was associated with future onset of chronic conditions (relative risk [RR] 2.2; 95% confidence interval [CI] 1.2 to 4.2) and with mortality (RR 2.6, 95% CI 1.2 to 6.2).[33]

Young adult survivors of childhood cancer experience frailty at rates similar to those observed in persons who are several decades older, for which rates from a meta-analysis of 44,894 persons aged 65 or older are reported to be 9.6% among women and 5.2% among men,[34] suggesting accelerated aging in the survivor population. Additional research is needed to examine this phenomenon so that survivors of childhood cancer at risk for frailty can be identified and appropriate interventions can be developed to prevent or remediate frailty among those at risk for poor health outcomes.

AGING AND COMORBIDITIES AMONG SURVIVORS DIAGNOSED WITH ADULT CANCERS

Most of the detailed longitudinal studies of cancer survivors have involved survivorship of patients with childhood cancer to midlife. However the incidence of cancer increases dramatically with increasing age and the great majority of cancer survivors are those who have experienced cancer as an adult. Thus, 60% of cancer survivors in the United States are over 65 years old and most of them have survived for 1 to 25 years.[35,36] Moreover, with the current rapid increase in the population aged 65 or older the number of cancers occurring in this segment of the population is expected to rise by 67% from 2010 to 2030, with a potential similar increase in the number of survivors.[37] These individuals are dealing with the interacting effects of the biologic and physiologic changes of aging, multimorbidity, after-effects of the cancer, and the effects of the cancer treatment.[38] Biologic aging involves changes in structure and function that lead to decreased reserve capacity and increased vulnerability to age-related diseases and overall forces of mortality. Characteristics of this process, which have been called the hallmarks of aging, include genetic instability with an imbalance in DNA damage and repair, telomere deterioration, epigenetic alterations, altered nutrient sensing, protein instability, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, and, most prominently, inflammation.[39,40]

These biologic changes lead to physiologic consequences that are largely manifested by declines in organ reserve capacity across virtually all organ systems and an overall decrease in homeostatic reserve. Although organ function generally remains adequate to accommodate the usual activities required for daily life, the decline leaves the aging individual vulnerable to any challenges to homeostasis. Such challenges would certainly include the effects of cancer and its treatment, which may have a lasting effect should the older patient survive.

Although some of the adverse effects may be caused by the cancer per se, for example, destruction of tissue as a result of direct tumor invasion in the context of decreased repair capacity, most appear to caused by the effects of the treatment. Surgery, radiation therapy, and hormone therapy can affect almost every system, but chemotherapy has the most pervasive effect. These long-term and late effects of treatment produce changes in function at the organ level that in many respects mimic those of aging (Table 1).[35] Compared with the young individual in whom such changes may produce a "premature aging syndrome," in the older adult these changes are superimposed on the age-related changes described above. At the cellular level the majority of chemotherapeutic drugs affect DNA, either through inhibition of DNA synthesis (e.g., antifolates, antipurines) or by inducing DNA damage (e.g., alkylating agents, platinum, topoisomerase inhibitors, anthracyclines). In the older adult this occurs in the setting of an age-related reduction in DNA damage repair, thus creating a negatively synergistic effect. Another drug effect of functional importance to the older cancer survivor occurs with drugs that bind to microtubules and disrupt their function (e.g., vinca alkaloids and taxanes). These drugs have particularly adverse effects on peripheral nerve tissue, which is nonrenewable, thus setting the older adult up for persistent and late effects of neural damage or diminished function.[41]

Two organ systems are particularly illustrative. A number of studies, predominantly in women receiving adjuvant treatment for breast cancer, have demonstrated declines in cardiovascular reserve capacity (CVRC).[42,43] Although some of these patients will experience recovery of function, the majority will sustain continuing reductions in CVRC. Older women, in whom the CVRC may already be diminished by age-related physiologic deterioration, may not have sufficient reserve capacity to withstand the additional stressors of cardiovascular pathologies (e.g., atherosclerotic cardiovascular disease). In this regard cardiovascular disease now appears to be the predominant cause of death in older women with early stage breast cancer.[42] Another example is neurotoxicity. Recent studies have indicated that symptoms of neuropathy, especially sensory symptoms in the lower extremities, persist for 2 to 11 years following the diagnosis and treatment of colorectal cancer, and that these symptoms are associated with worse health-related quality of life (HRQOL) and physical function.[44] For older individuals changes (cardiovascular, neural, and others) that lead to decline in physical function are particularly problematic because they may lead to loss of independence, one of the most feared outcomes. The additional burden of multiple comorbidities creates a perfect storm for potential adverse outcomes in older survivors.

The result of these various interacting factors is that older

cancer survivors do indeed have a higher prevalence of functional imitations and poorer quality of life than older adults without cancer.[45,46] The effect on HRQOL varies among cancer types, with survivors of cervical, colorectal, and hematologic cancer faring worse than those surviving breast and prostate cancer.[46] The good news is that for very long term breast cancer survivors (e.g., more than 15 years) the HRQOL and functional status appears to approach that of similar aged individuals without a cancer history.[46-48] Thus the effect of cancer and its treatment appears to be ameliorated over time, and clinical status becomes determined more by age-related changes and chronic comorbidities.

INTERVENTIONS TO IMPROVE OUTCOMES FOR AGING CANCER SURVIVORS

The Institute of Medicine (IOM) has highlighted the fact that cancer survivors are a high-risk, growing population of individuals that require specialized health care throughout their life span.[49,50] The 2006 IOM report highlighted the need for all cancer survivors and their primary care providers (PCPs) to be provided with a survivorship care plan, which represents a road map for post-treatment care created by their oncology treatment team.[50] However, the majority of cancer survivors are not followed at a cancer center, are not receiving recommended risk-based health care or surveillance, are unaware of their risks, and are followed by community-based health care providers, many of who are understandably unfamiliar with the health risks of cancer survivors.[51-57] Further, most survivors and their PCPs report that they have never received a treatment summary.[52,54,57] All of these factors must be considered when developing interventions aimed at encouraging healthy lifestyles and risk-based health care.

Over 25% of childhood cancer survivors in the North American cohort of the CCSS report having smoked over 100 cigarettes in their lifetime and 17% report being current smokers.[58] As smoking may influence the incidence and severity of late effects in this population, the first intervention studies in cancer survivors have focused on smoking cessation. The Partnership for Health (PFH) study aimed to promote smoking cessation in 796 survivors of childhood cancer in the CCSS who identified themselves as smokers. Participants were randomly assigned to either a self-help intervention or a peer-counseling intervention. Ultimately, 15% of all participants had quit smoking at the initial 8-month follow up. Controlling for baseline self-efficacy and depression, participants in the peer-counseling intervention group were twice as likely to quit smoking by the 12-month follow up than those in the self-help group (odds ratio, 1.99; 95% CI, 1.27 to 3.14).[59] This study was followed up by the PHS-2 study, in which 374 smokers from five survivorship clinics were randomized to either a Web-based or print format of the PFH intervention. This study showed no differences in quit rates or readiness to quit in either arm.[60] In addition, Klesges et al. at St. Jude Children's Research Hospital have initiated a tobacco use intervention study funded by the National Cancer Institute (NCI) examining recruits from the St. Jude quit line within the CCSS and the St. Jude After Completion of Therapy clinic (R01CA127964).[61] This is a randomized controlled clinical trial that will examine the long-term (1-year) efficacy of a counselor-initiated versus participant-initiated tobacco quit line with adjunctive nicotine replacement therapy in both groups. The primary outcome measure is cotinine-validated self-reported smoking abstinence at 1-year follow-up. This study is ongoing.

Given the rates of obesity and cardiovascular disease in cancer survivors, diet and exercise interventions are an important focus for survivorship researchers. Smith et al. reported a pilot study that examined an home-based aerobic exercise and strength training intervention in five adult childhood cancer survivors who are part of the St. Jude Lifetime Cohort.[62] Body composition, strength, and cardiopulmonary fitness were evaluated before and after the 12-week intervention. All five patients completed the study and 86% were compliant with exercise. To date, no large randomized diet or exercise intervention studies have been reported in childhood, adolescent, or young adult cancer survivors. Furthermore, no studies targeting cancer survivors that focus specifically on improving frailty, i.e., increasing muscle mass, have been reported.

Modification of lifestyle factors to improve patient quality of life is also a focus of work with older cancer survivors. A recent randomized trial in older cancer survivors using telephone counseling and mailed materials on diet and exercise has demonstrated that physical function and HRQOL can be improved over the course of 1 year, and that these improved health behaviors, body mass index, and physical function can be at least partially sustained 1 year after cessation of the intervention.[63,64] Thus, it is possible that practical programs designed to provide ongoing interventions could substantially improve QOL in older cancer survivors and should perhaps be incorporated into Geriatric Survivorship Care Plans.

In addition to improving lifestyle behaviors, most adult survivors of childhood cancer are not engaged in recommended life-long risk–based health care and surveillance. For example, women who were previously exposed to chest radiation have a risk of breast cancer as high as 20% by age 45 and therefore the Children's Oncology Group and American Cancer Society recommend early breast cancer surveillance with mammography and breast MRI in these women.[65,66] Despite these recommendations, a 2009 report examining the breast cancer surveillance practices of 551 women who were exposed to chest radiation for childhood cancer showed that only 36.5% had undergone mammography in the preceding 2 years.[55] There are currently three NCI-funded intervention studies targeted at: (1) improving breast cancer surveillance rates in women exposed to chest radiation for a childhood cancer (EMPOWER); (2) improving cardiovascular screening among childhood cancer survivors treated with cardiotoxic therapy (ECHOS); and (3) improving skin protection and skin cancer detection among survivors treated with radiation. These studies are ongoing. As most aging sur-

vivors have multiple chronic health issues, it will be important to develop intervention studies aimed at these multiple morbidities. Furthermore, as noted, one of the first steps would be for all survivors to have a Survivorship Care Plan (as endorsed by the IOM and Commission on Cancer).[50,67] Because studies have shown that most survivors and their physicians do not possess a Survivorship Care Plan, studies should focus on creation and dissemination of these documents. Moreover, the unique challenges of older cancer survivors must be considered. Although Survivorship Care Plans are intended to ensure optimal long-term follow-up care, they tend to concentrate on cancer-related factors rather than the abovementioned age-related changes that eventually dominate the picture.[68] Geriatric Survivorship Care Plans that provide guidance on the management of these geriatric issues (e.g., comorbidities, functional change, geriatric syndromes) may prove to be helpful.[38]

In summary, the interplay of cancer and aging is complex and we are only beginning to understand its effect on the growing cancer survivorship population. Research focused on the issues of cancer survivorship and tobacco cessation, diet, exercise, and health care will be imperative to mitigate the influences of chronic health issues associated with both cancer and aging in the survivorship population. To date, ASCO has tremendous efforts focused in these areas, including tobacco cessation and obesity. ASCO's tobacco cessation resources are available at www.asco.org/practice-research/tobacco-cessation-and-control-resources. In 2013 ASCO brought together an Energy Balance Working Group comprised of Cancer Prevention and Survivorship Committee members to develop a number of ASCO initiatives on obesity and cancer. The Working Group is currently developing a toolkit for patients and providers to inform both groups about the data demonstrating a link between obesity and cancer risk and outcomes, and to help providers assist their patients in initiating weight management strategies after cancer diagnosis and throughout the cancer care spectrum. Finally, ASCO is working to develop resources, including a toolkit for oncologists and primary care physicians, to ensure that appropriate survivorship care is delivered to all survivors.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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