Impact of Survivorship-Based Research on Defining Clinical Care Guidelines

Melissa M. Hudson¹, Wendy Landier², and Patricia A. Ganz³

Abstract

The growing number of individuals living five or more years from cancer diagnosis underscores the importance of providing guidance about potential late treatment effects to clinicians caring for long-term cancer survivors. Late treatment effects are commonly experienced by cancer survivors, increase in prevalence with aging, produce substantial morbidity, and predispose to early mortality. Findings from survivorship research permit providers to anticipate health risks among predisposed survivors and facilitate their access to interventions to prevent, detect, or rehabilitate cancer-related morbidity. This article reviews the impact that survivorship research has made in defining clinical care guidelines and the challenges that remain in developing and translating research findings into health screening recommendations that can optimize the quality and duration of survival after cancer. Cancer Epidemiol Biomarkers Prev; 20(10); 2085–92. ©2011 AACR.

Introduction

Progress in early detection and treatment of cancer has produced a growing population of long-term survivors, estimated to approach 12 million based on a recent analysis of 2007 follow-up data from the Surveillance, Epidemiology, and End Results (SEER) programs (¹). With nearly 65% of individuals living 5 or more years from diagnosis, efforts to address the health issues of long-term cancer survivors have become increasingly important to optimize the duration and quality of their survival (¹). Cancer and its treatment predispose survivors to a variety of adverse outcomes, with some complications presenting early in the clinical course following diagnosis and initiation of therapy and others manifesting years after completion of therapy. Chronic cancer treatment-related effects are commonly experienced by cancer survivors, increase in prevalence with aging, and result in substantial morbidity and early mortality (²–⁶). Outcomes research among cancer survivors has been critical in identifying survivors at risk for adverse treatment effects. Knowledge gained from these initiatives permits providers to anticipate health risks among predisposed survivors and facilitate their access to interventions to prevent, detect, or rehabilitate cancer-related morbidity. Recognition of the significant risks for treatment-related complications has generated the call for development of clinical practice guidelines to standardize and enhance cancer survivor follow-up care. However, the lack of high-level evidence supporting a reduction in morbidity and mortality associated with screening have substantially hindered these efforts. The significant improvement in long-term survival for both pediatric and adult onset malignancies, coupled with compelling evidence linking specific exposures with adverse outcomes, has motivated efforts to develop guidance for practitioners to facilitate identification, management, and prevention of cancer treatment-related effects in long-term survivors. This article will review methodologic issues related to screening and surveillance, efforts undertaken to develop screening and surveillance guidelines for the management of survivors of pediatric and adult malignancies, and priorities for future research. In this article, the term “screening” is used to describe evaluations done for the purposes of detecting treatment-related sequelae in asymptomatic cancer survivors, whereas the term “surveillance” is used to describe evaluations done for the purposes of detecting recurrent malignancy in these survivors.

Screening Methodologies

Screening is a secondary prevention measure aimed at early detection of and intervention for health conditions that place patients at significant risk for morbidity and mortality (⁷). The goal of screening is to identify individuals likely to have the targeted health condition at an early stage, confirming the diagnosis with further testing and intervening early with a treatment that offers an advantage over treatment initiated when the condition
is clinically apparent. Several factors are routinely considered in research evaluating screening methodologies, including the prevalence and severity of the health condition, the sensitivity, specificity, predictive value, and costs of the available screening measures, the number needed to be screened for a given duration to prevent one death or adverse event (8), the potential benefits and harms of screening to individuals and society, the interventions available if the health condition is detected, and the potential reduction in morbidity and mortality associated with early detection of the health condition.

In order for a screening program to be cost effective, the prevalence of preclinical disease in the targeted population must be relatively high, the targeted condition must have a detectable preclinical phase, and the consequences of the untreated health condition must be of sufficient severity to outweigh the potential harms of screening (9). A suitable screening test must have valid, reliable, and reproducible results (10). Sensitivity and specificity are measures of test validity. High sensitivity is associated with a low proportion of false negative results, whereas high specificity is associated with a low proportion of false positive results (11). Decisions about criteria for sensitivity and specificity involve a trade-off between undetected cases (false negatives) and erroneous classification of healthy individuals as having the condition (false positives; Ref. 9). Reliability is determined by consistency and reproducibility of results of repeated tests conducted on the same individuals under the identical test conditions. The positive predictive value (yield) of the screening modality is determined by the sensitivity and specificity of the test in combination with the prevalence of the condition in the population (9).

Screening is generally offered with an implicit promise that those undergoing testing stand to benefit. However, not all individuals benefit, and potential harms associated with screening include costs, procedure-related risks, anxiety, and (if results are false negative) the potential for false reassurance and delayed diagnosis (12). In order for a screening program to be efficacious, a treatment must be available that can be applied more effectively when the targeted health condition is detected at an earlier stage (i.e., when the condition is asymptomatic) rather than when the condition is clinically apparent (9). Thus, if the prognosis is equally good (or equally bad) whether treatment is initiated during the presymptomatic or symptomatic phases, screening is not indicated (9).

The most important aspect of a screening program is arguably its effectiveness in reducing morbidity and mortality from the targeted condition in the population of interest (9). Potential measures of efficacy include severity of disease at time of diagnosis and duration of survival; however, severity of disease can be affected by selection bias of program participants, and duration of survival can be affected by lead-time bias (i.e., detection of disease earlier in its natural course as a result of screening). Therefore, the most definitive measure of efficacy of a screening program is comparison of cause-specific mortality rates in those diagnosed by screening versus those diagnosed when the disease becomes clinically apparent (9).

Translating the public health tenets of screening to a cancer population at risk for a specific treatment-related toxicity is complicated by difficulty in characterizing the clinical features of a group that would benefit from screening. For example, anthracyclines have a well-established dose-related risk of cardiomyopathy, but other factors such as age at treatment, gender, time from exposure, treatment with other cardiotoxic modalities (e.g., radiation) and genetics have been variably reported to influence risk for presentation of clinically significant cardiac dysfunction (13). Moreover, left ventricular systolic dysfunction, as measured by readily available modalities such as echocardiography, is a late event in the clinical presentation of cardiomyopathy and thus may not be an optimal screening modality to sensitively detect preclinical disease (13). Consequently, the utility of screening asymptomatic survivors exposed to lower cumulative anthracycline doses is unclear. Although it is important that providers be aware of this potential risk, counsel survivors about the importance of adherence to a heart healthy lifestyle, and assess for comorbid conditions that may affect risk of cardiac disease (e.g., overweight, hypertension, diabetes, and dyslipidemia), future research is needed to better characterize an asymptomatic group exposed to anthracyclines who would derive the most benefit from screening, as well as the appropriate time to initiate screening and the most sensitive/specific modality and frequency of screening.

In contrast, there is compelling data about the risk of breast cancer among young women treated with chest radiation, which approaches 20% at 40 years of age (14, 15). The risk is comparable with that observed for women with a BRCA gene mutation, whose cumulative incidence of breast cancer ranges from 10% to 19% by age 40 years (16). Cohort studies have shown that breast cancer risk is elevated 10 to 25 years before the age when routine screening is recommended in general population—providing support for earlier screening in this population (15). The median time to diagnosis of breast cancer from radiation exposure is 15 to 20 years, with cases being diagnosed as early as 8 years from exposure. Mammography can detect most cancers but may be limited in sensitivity in women with moderate to very dense breast tissue (17). Compared with mammography, MRI has a higher sensitivity in detecting invasive cancer than mammography, but mammography seems to be more sensitive than MRI in detecting ductal carcinoma in situ (17). These data have directly informed recommendations for breast cancer screening in this high-risk population, in whom outcomes after breast cancer diagnosis can be optimized by early detection (15).

As these 2 very discrete examples suggest, the quality and level of evidence to make specific screening recommendations and guidelines in cancer survivors varies substantially. In the discussion that follows, we highlight...
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strategies that have been used to translate survivorship research findings into clinical guidelines for health screening in survivors.

Health Screening Recommendations for Long-term Survivors of Pediatric Malignancies

Over the last 30 years, steady improvement in survival for pediatric malignancies has provided opportunities for late health outcomes investigations that characterized groups at risk for morbidity and mortality related to specific host factors and therapeutic exposures. This information guided successive primary therapy modifications aiming to prevent or reduce cancer-related toxicity in newly diagnosed patients and secondary interventions aiming to promote early detection and access to remedial services among long-term survivors predisposed to morbidity. The emerging appreciation of the multifactorial nature of cancer-related morbidity in pediatric cancer survivors led to the recommendation for risk-based, survivor-focused care which includes 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 (18, 19). This care is optimally coordinated through a multidisciplinary long-term follow-up program that organizes a survivorship care plan and works collaboratively with community physicians in a shared-care model (20). A comprehensive survivorship care plan includes information about cancer diagnosis (histology, involved tissues/organs), specific treatment (surgical procedures, chemotherapeutic agents, radiation treatment fields and doses, hematopoietic cell transplant, and blood product transfusion), cancer-related health risks, and recommendations for health screening and risk-reducing interventions.

Unfortunately, because of age, geographic, or financial restrictions, the majority of childhood cancer survivors do not have access to late effects experts in long-term follow-up programs to coordinate their care as the contact of survivor with the cancer center becomes less frequent with increasing passage of time from diagnosis and therapy (21). Among Childhood Cancer Survivor Study participants (median age, 31.4 years), 88.8% reported receiving some form of medical care in the preceding 2 years, but only 31.5% reported receiving care that focused on their prior cancer (survivor-focused care), and 17.8% reported survivor-focused care that included advice about risk reduction or discussion or ordering of screening tests (22). These data underscore the need for readily available resources to guide risk-based, survivor-focused care by busy community clinicians unfamiliar with the unique health risks of childhood cancer survivors.

Developing screening recommendations for survivors of childhood, adolescent, and young adult malignancies poses unique challenges. Although well-conducted studies on large populations of childhood cancer survivors clearly show evidence linking specific therapeutic exposures and adverse outcomes, high-quality evidence to characterize risk groups and support specific screening recommendations is not available for most outcomes studied. Factors contributing to this deficiency include lack of standard definitions of toxicity, use of variable testing strategies, and inconsistency in evaluation time in relation to therapeutic exposures. In addition, late health outcomes investigations of childhood cancer survivors are often limited by participation bias due to lack of access to survivors who are lost to follow-up or no longer followed at the cancer center. Finally, because of the relatively small size of the pediatric cancer survivor population and the delayed time to onset of many therapy-related complications, undertaking randomized studies in asymptomatic survivors to assess the impact of screening recommendations on the morbidity and mortality associated with the late effect is not feasible. These same issues also complicate the implementation of studies evaluating utility and cost-effectiveness of screening asymptomatic survivors.

The immediate needs of the medically vulnerable and growing population of childhood cancer survivors prompted the use of a hybrid model for the development of health screening recommendations by several pediatric cooperative groups (23–26). Group methods varied in the magnitude and scope of the literature review, which provided evidence linking late effects with therapeutic exposures. However, all proposed screening recommendations are based on the clinical experience of late effects experts, matching the magnitude of the risk with the intensity of the screening recommendations. Strategies used by the pediatric cooperative groups in the development, implementation, dissemination, and maintenance of health screening recommendations for childhood cancer survivors are summarized in Table 1 (23–26). In general, these initiatives include guidance for screening of potential medical and psychosocial treatment effects, define clinical and treatment characteristics that influence risk, offer suggestions for further evaluation of survivors with positive screening results, and delineate health-promoting interventions/counseling to enhance survivor outcomes. Collaborative efforts are ongoing to harmonize screening recommendations for key outcomes and identify knowledge gaps to address in future research. Additional research is needed to establish that screening and intervention for specific cancer-related complications is feasible, efficacious, and ultimately benefits survivors by minimizing or preventing late effects.

Long-term follow-up practices for childhood cancer survivors vary internationally on basis of the resources of the health care system, but generally, a formal transition back to primary care is rare in most settings. Because of the transition of care imposed upon the vast majority of childhood cancer survivors when they "age
Table 1. Pediatric cooperative group strategies for development, implementation, dissemination, and maintenance of health screening guidelines for childhood cancer survivors

<table>
<thead>
<tr>
<th>Establish aims and goals of guidelines</th>
<th>Provide guidance to clinicians caring for survivors.</th>
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<tbody>
<tr>
<td></td>
<td>Standardize and enhance follow-up care of survivors.</td>
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<td></td>
<td>Facilitate early identification of late treatment effects.</td>
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<tr>
<td></td>
<td>Promote timely intervention for late treatment effects.</td>
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<td></td>
<td>Educate survivors and families about health risks.</td>
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<td></td>
<td>Promote healthy lifestyle of survivors.</td>
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| Define target population for screening | By age at diagnosis (childhood, adolescent, young adult, and adult). |
|  | By time from completion of therapy (≥2 years, ≥5 years, etc.). |
|  | By disease status (maintained remission, stable disease, etc.). |

| Consider intended users of guidelines | Hematology/oncology providers (pediatric/medical, surgical, radiation, nursing, etc.). |
|  | Primary care providers (pediatricians, family physicians, internist, and gynecologists). |
|  | Subspecialty providers (pediatric/medical, endocrine, cardiology, etc.). |
|  | Cancer survivors and families. |

| Identify expertise required to develop the guidelines | Hematology/oncology (pediatric/medical, surgery, radiation, nursing, and transplant). |
|  | Primary care (pediatrics, family medicine, internal medicine, and gynecology). |
|  | Subspecialty (pediatric/medical, endocrine, cardiology, etc.). |
|  | Behavioral (psychology, social work). |
|  | Supportive care (physical/occupational therapy, etc.). |
|  | Patient/survivorship advocacy. |
|  | Analytical (epidemiology, biostatistics, and public health services). |

|  | Translation of evidence and clinical experience into screening recommendations. |

| Determine preferred guideline design | Therapy/exposure based |
|  | Outcome based (by organ, tissue, or function) |
|  | Disease based |

| Establish guideline content | Address both medical and psychosocial outcomes. |
|  | Comprehensive versus selected key late effects. |
|  | Organization/venue of long-term follow-up care. |
|  | Provider versus survivor (patient education) format. |
|  | Treatment summary template. |
|  | Medical citations to support recommendations. |

| Implement and disseminate guidelines | Posting on internet website. |
|  | Presentations at cooperative group and professional society meetings. |
|  | Presentations in academic and community forums. |
|  | Publication of review manuscripts. |
|  | Incorporation into primary care pathways. |
|  | Collaboration with health care and insurance organizations. |

| Organize plan to maintain currency of guidelines | Ongoing monitoring of late effects literature. |
|  | Biennial systematic review by multidisciplinary task forces. |
|  | Consideration of guideline revisions by oversight committee. |
|  | International collaboration to harmonize recommendations. |

Guidelines from the following Pediatric Cooperative Groups were reviewed for inclusion in this summary: Children’s Oncology Group (COG; ref. 25), Children’s Cancer and Leukemia Group (CCLG; ref. 23), Dutch Childhood Oncology Group (DCOG; ref. 26), and Scottish Intercollegiate Guidelines Network (SIGN; ref. 24).
out” of follow-up at pediatric cancer centers, pediatric oncologists have also begun to explore models of survivorship care that integrate procedures to optimize education of primary care physicians who will ultimately be responsible for delivery non–cancer-related care and methods to keep medically vulnerable survivors engaged in long-term follow-up care (27–31). A key aspect of these models is ongoing communication with the primary care physician and delineation of responsibilities in regards to surveillance and screening after completion of cancer therapy. The levels of survivorship care proposed within these models correlate the location and frequency of follow-up care with intensity of therapy, reserving center follow-up for those at greatest risk of adverse outcomes (Table 2; Refs. 28, 30, 31). Research from countries with national health care plans support the willingness of primary care providers to participate in programs that share care with pediatric oncology centers (32, 33). Recent studies also affirm that adults treated for childhood cancer can be reengaged and recruited to participate in long-term follow-up care programs (34–36).

Health Monitoring/Surveillance
Recommendations for Long-Term Survivors of Adult-Onset Malignancies

With the growing number of adult cancer survivors, there has been increasing awareness of the need to improve upon the follow-up care for these individuals. Up until a few years ago, most follow-up care for adult cancer survivors was focused on surveillance for cancer recurrence, largely derived from clinical trial follow-up protocols (e.g., monitoring with scans and blood work). In common diseases such as breast and colon cancer, in which adjuvant therapy is used and long-term survival is expected, specific surveillance guidelines have been developed by the American Society of Clinical Oncology (ASCO; Refs. 37, 38). For the breast cancer guideline, high level randomized controlled trial evidence was available supporting a recommendation for only breast imaging with mammogram and clinical examinations at limited frequency (38). These guidelines do not address health promotion, primary or secondary cancer prevention, or symptom management of common long-term and late effects. The challenge in adult oncology is the many different kinds of cancers beyond breast and colon cancer, for which no systematic guidance is available for cancer recurrence surveillance, and with ad hoc consensus recommendations being the rule. A popular example of this is the use of disease specific pathways for follow-up care that have been developed by the National Comprehensive Cancer Network (NCCN; www.nccn.org), which are consensus based from disease experts at leading cancer centers.

In 2005, with the release of the Institute of Medicine (IOM) report on adult cancer survivors (39), there was an acceleration in efforts to go beyond cancer surveillance as part of follow-up care. This report and two before it from the President’s Cancer Panel (2003-04) “Living Beyond Cancer: Finding a New Balance”(40), as well as a CDC report from April 2004 “A National Action Plan for Survivorship: Advancing Public Health Strategies,”(41) focused on the burden of physical and psychological outcomes in cancer survivors, and the need to address these in a systematic way. Among the suggestions emanating from these reports was the importance of coordinating post-treatment care, and the need to address persisting symptoms, anticipate potential late effects of cancer treatment, develop mitigating strategies for known treatment risks and planning for unanticipated problems.

### Table 2. Levels of long-term follow-up care for childhood cancer survivors

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<tr>
<th>Risk of late effects</th>
<th>Proposed levels of follow-up care</th>
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<tr>
<td>Low</td>
<td>- Postal or telephone follow-up every 1 to 2 years.</td>
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<td>- Single visit with cancer center long-term follow-up program followed by ongoing monitoring by primary care provider, according to follow-up plan established by cancer center.</td>
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<td>Surgery only; low-risk chemotherapy (excluding alkylators, anthracyclines, bleomycin, and epipodophyllotoxins)</td>
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<tr>
<td>Moderate</td>
<td>- Follow-up every 1 to 2 years with nurse or primary care physician.</td>
</tr>
<tr>
<td>Other than high/low risk</td>
<td>- Initial follow-up at cancer center for 5 to 10 years, followed by transition to primary care provider, who carries out ongoing monitoring according to follow-up plan established by cancer center.</td>
</tr>
<tr>
<td>High</td>
<td>- Ongoing annual follow-up in specialized long-term follow-up program at cancer center.</td>
</tr>
<tr>
<td>Hematopoietic cell transplant; high-dose anthracyclines or alkylating agents; radiation ≥24 Gy</td>
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*Long-term follow-up begins 2 years following completion of therapy. Adapted from references 27–31.*
(e.g. fertility preservation), and for maximizing the health and well-being of survivors. A key element that emerged was the concept of a treatment summary and survivorship care plan, to be shared with the survivor and his/her physicians, so that the past cancer treatments could be spelled out with guidance for future care related to specific exposures, e.g. radiation to the head and neck area and resultant hypothyroidism several years later.

Current efforts in adult survivorship care have begun to focus on testing new models for delivery of survivorship care and coordination between primary care providers and oncology specialists (42–45). The challenge has been to identify who on the cancer care team will take responsibility for completing a treatment summary and care plan when treatment ends, as well as determining the best timing to do this. There are some natural transition points in some diseases, for example in prostate cancer, at the completion of radiation therapy, or in breast cancer patients at the end of adjuvant chemotherapy and radiation therapy. However, for diseases like high grade lymphoma or sarcoma, waiting for 18-24 months after the completion of primary treatment might be best, to ensure that the patient has been rendered disease-free and needs more limited cancer recurrence surveillance. Importantly, there are no defined times when these transitions occur for the vast majority of adult cancer patients. As a result, many clinicians are considering the development of risk-based strategies for the intensity of oncology follow-up care. For example, patients with very low risk breast cancer or colon cancer may not need close supervision by an oncology specialist, and can have all of their follow-up care assumed by a primary care provider, if he or she feels comfortable with this. This is where the treatment summary and care plan can be most helpful (46).

Unfortunately, during the past several decades, adult cancer patients and survivors have remained under the long-term care of oncology specialists, and thus many primary care providers (PCP) lack self-efficacy (knowledge and perceived skills) to care for these patients (47). In the IOM report (39, 48, 49), there was extensive discussion of applying a shared care model to improve the posttreatment coordination of care for cancer survivors. This model is often practiced in other complex health conditions (e.g., neurologic disorders, heart disease, arthritis), in which the primary care provider takes care of the other chronic conditions a patient has, as well as addresses health promotion and disease prevention (e.g., monitoring lipids and blood pressure, immunizations, smoking cessation)—the latter are activities that are routine for the PCP, but may not be addressed in oncology follow-up visits with cancer survivors in the oncology setting. Work done by several investigators with the SEER-Medicare database suggests that cancer survivors are more likely to receive guideline-based general health care when both an oncologist and PCP are involved (50–53).

Although it has been more than 5 years since the call for better coordination of post-treatment care for adult cancer survivors, there is a limited amount of new level I randomized controlled trial data on cancer surveillance follow-up care. However, there is sufficient consensus on best practices for the major cancer sites (see NCCN guidelines), and if applied uniformly, both overuse and underuse of cancer surveillance testing might be prevented (54). More important, there are many evidence-based guidelines for general medical care, for example, osteoporosis prevention and treatment, monitoring for cardiovascular risk and diabetes, age-related health screenings and immunizations, which need to be offered to cancer survivors, who may in fact be at risk for accelerated aging of late consequences of treatment if this comorbid health risks are not properly managed (55, 56). Cancer survivors who are exclusively cared for in oncology settings are unlikely to have these health-promoting and disease-preventing strategies offered to them, as we know that the health habits of cancer survivors do not differ from the general population—they are overweight and have other poor health habits (57, 58). Even when cancer patients are comanaged with a PCP, those clinicians may not appreciate the importance of applying health promotion in cancer survivors. With regard to long-term and late effects of cancer therapy, ASCO has fertility recommendations (59) and an evidence review on cardiac and pulmonary late effects (60), but as yet, it has not found an effective mechanism to provide guidance on how future risks from treatment exposures should be handled.

Summary

Due to the significant advances in cancer therapeutics achieved over the last 30 years, the majority of individuals will survive 5 or more years after the diagnosis of cancer. The duration and quality of that survival will be determined by the ability of clinicians to optimize cancer control efforts and minimize cancer-related toxicity. Historically, survivorship research has played an important role in improving long-term outcomes by guiding primary and secondary health-promoting interventions focusing on newly diagnosed cancer patients and cancer survivors predisposed to morbidity following specific therapeutic interventions. Ongoing research initiatives are evaluating how to translate currently available knowledge about survivorship outcomes to effectively and efficiently guide clinical care in both oncology and primary care venues. Considering the spectrum of cancer-related treatment effects and limited resources for survivorship research, prioritization of research initiatives focusing on highly prevalent, life-threatening and/or potentially remediable toxicity will be important. Likewise, keeping clinicians and providers engaged in research to characterize late toxicity risk profiles of new agents and the multifactorial contributions of cancer treatment, genetics, health behavior,
and aging to long-term morbidity represents a challenge that must be overcome to optimize quality of survival after treatment for cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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