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Patient Surveillance After Cancer Treatment

Humana Press

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To our families, whose support made the creation of this book feasible.

To our colleagues, whose research findings we incorporated in writing this book.

To our patients, whose care this book is intended to improve.

To Judith Ann Feldworth, the Saint Louis University editor, whose skill, tenacity, and creativity over several years made this book a reality.

Preface

Cancer remains a major cause of death worldwide. With modern therapy, millions of patients can expect (or at least hope) to be cured. With the passage of time, a proportion of these cancer survivors experience recurrence. Some die and some are rescued by further interventions. Some sustain complications of treatment which are merely annoying; others are fatal. These considerations show that cancer patient care is an important topic, but it is presently underresearched and underappreciated. The primary focus of this book is patient surveillance after curative-intent initial treatment. It is my second book devoted to this topic. The format is somewhat different from the first (*Cancer Patient Follow-up*, Mosby, 1997). The secondary focus of the book is to publicize the need for well-designed, adequately powered randomized clinical trials comparing two (or more) surveillance strategies for each type of cancer. Currently the National Institutes of Health and other major sources of funding in America do sponsor research about the clinical course of cancer patients after treatment but do not support such trials. Clinicians, patients, and society as a whole are harmed by this. Clinicians lack high-quality evidence upon which to base surveillance for their patients. Patients are subjected to diagnostic tests that are utilized at remarkably different rates, even by expert physicians. This is prima facie evidence of overuse and/or underuse of resources, with significant risk of misuse as well. In order to rationalize surveillance, we believe that patients, physicians, the public health community, advocacy groups, payers, and others will need to advocate for enabling legislation that requires such trials. The Medical Research Council of the United Kingdom and similar agencies in other European countries have already accepted this premise, and the trial results have changed medical practice. Such trials are expensive. They typically take years to accrue a sufficient number of patients, and several more years to mature and yield results. Successor trials will be required as new salvage therapies enter clinical practice, better methods of prevention and early detection are devised, toxic effects of therapy are avoided or mitigated, and so on.

Saint Louis, MO, USA — Frank E. Johnson, MD

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Overview

1

David Y. Johnson and Frank E. Johnson

Keywords
AHCPR • Cancer • Guidelines • Postoperative surveillance • Protocol

Self-awareness is a particularly human trait. When it evolved, proto-humans became aware that they were destined to die. When language evolved, they were able to share this understanding with others. When written languages were developed, their thoughts about mortality were recorded in permanent form. The documents that have survived to the present convincingly demonstrate that humans have sought to understand why they become ill and die for a very long time. Cancer, in its many forms, is featured in the earliest of these documents [1]. It is feared and many forms of treatment have been employed throughout the ages, almost all of which were unsuccessful. By the nineteenth century, with the introduction of effective anesthesia, relatively safe major surgery became feasible. As a result, for the first time in history some patients with cancer were cured [2]. This created a cohort of cancer survivors. Shortly thereafter, it became clear that this population is prone to recurrence of the index cancer and/or new primary cancers and/or adverse effects of therapy. Treatments often failed, however, and major medical texts in the early-twentieth century made no mention of second primary cancers [3,4] but adverse effects of therapy were well known. This soon led to the concept of postoperative surveillance. This was facilitated in the late nineteenth century by the development of diagnostic x-rays [5]. Cancer patients also benefited by the introduction of radiation as a powerful treatment. Its hazards soon were recognized and those who had received radiation therapy as the initial treatment were soon candidates for surveillance. Relapse often occurred, as for those treated with surgery. Effective systemic therapy (oophorectomy for metastatic breast cancer) had its start in the late nineteenth century also [6]. The complications of this operation were presumably infrequent and manageable, but surveillance was probably carried out to determine how useful this novel form of therapy would be—since the concept of "chemical messengers" (hormones) was unknown until secretin was discovered in 1906 [7,8]. By the time effective systemic cytotoxic therapy was introduced into practice in the mid-twentieth century, the idea that it might eventually be curative was imagined by the few medical oncologists of that time and became a reality shortly thereafter, providing another cohort of survivors. The use of cytotoxic chemotherapy was regulated by regimen-specific drug administration protocols and institutional review boards (both novel concepts at that time). The post-treatment course was carefully documented. Documentation of initial disease status and estimation of prognosis were improved by the introduction of systematic staging methods such as the Federation Internationale de Gynecologie et d'Obstetrique and American Joint Committee on Cancer-Union for International Cancer Control systems. These common descriptors improved data collection and analysis. Introduction of new diagnostic testing modalities (serologic tumor marker measurement, computer-assisted tomography, magnetic resonance imaging, monoclonal antibody-based cellular stains, and the like) found immediate application in surveillance.

Medical practice, including cancer screening, diagnosis, staging, treatment, and posttreatment management, became rather complex in the twentieth century. The complexity led to

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increasing reliance on guidelines. From the time of the Edwin Smith Papyrus [1], informal health-related guidelines, often generated by untrained citizens and promoted by churches, schools, government agencies, and the like, have been used. These included advice about diet, behavior, hazardous materials, and so on. In recent times, guideline development has become much more rigorous and evidence-based. The U.S. Institute of Medicine published a book about this topic in 1990 [9]. It provided advice to the U.S. Agency for Health Care Policy and Research (AHCPR), particularly its Forum for Quality and Effectiveness in Health Care. The AHCPR and many other interested parties helped another Institute of Medicine committee formulate ways to develop guidelines [10]. This included methods to precisely define relevant terms, estimation of strengths and weaknesses of guideline development efforts, and so on. The books were produced by outstanding groups of experts who recognized that clinical practice guidelines had been used in various ways by some organizations to consider "costs, quality, access, patient empowerment, professional autonomy, medical liability, rationing, competition, benefit design, utilization variation, bureaucratic micromanagement of health care, and more" [11]. The authors intended to utilize a systematic approach, consider the evidence base, and evaluate the processes, structures, and incentives that contribute to the effectiveness and periodic evaluation of such guidelines. The 1992 book detailed desirable attributes of clinical practice guidelines: validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, a multidisciplinary development process, scheduled review, documentation of the process of guideline development, sensitivity, specificity, patient responsiveness, readability, minimum obtrusiveness, feasibility, computer compatibility, and appeals criteria [12]. All medical guidelines available today fail to possess some of these attributes; many fail to possess most of them. The Institute of Medicine experts exerted much effort to evaluate the state of the evidence supporting medical care. David Eddy, a very influential thought leader and a member of the Institute of Medicine, recognized three levels of appropriate medical care, related directly to the importance of the outcomes to patients and the persuasiveness and clarity of the evidence. In his analysis, when the evidence in favor of a particular course of care is very strong, the course can be termed a "standard" and recommended to all patients with only a few exceptions. When the evidence is not very strong, the course can be termed a "guideline." A guideline applies in most situations but with more exceptions than are warranted for standards. The term "option" refers to a course of management in which the evidence does not warrant specific recommendations [13]. The Institute of Medicine committee also explained the meaning of terms such as "strong evidence," "strong consensus," and the like. They recognized that consensus statements generated by experts have some value.

Table 1.1 Hypothetical distribution of evidence and consensus for all health services and patient management strategies

Strength of evidence	Strength of consensus	Percentage of all services
++	++	2
++	+	2
++	0	0
+	++	20
+	+	25
+	0	0
0	++	20
0	+	25
0	0	6

++ = strong evidence or consensus
+ = modest evidence or consensus
0 = very weak or no evidence or consensus
From Ref. [15]

The reliability of consensus-based guidelines has increasingly been questioned, however. A major reason is the near-inevitability of conflict of interest among those who create guidelines of most sorts. Those who create guidelines are always well-informed about the topic at hand. They usually have carried out research about that particular topic. They have often served as paid consultants to for-profit companies. Some have participated in industry-sponsored research. Even if these individuals agree to abstain from voting on guidelines during the process of creating them, their comments during the development process are often quite persuasive [14]. The committee also recognized that many courses of care in medical practice are not supported by good evidence. The committee estimated how evidence of variable quality and consensus of variable strength are distributed among all courses of care in healthcare systems [15] (Table 1.1).

Since publication of these two very influential books, interest in guidelines has increased. There has also been an explosion in the number of guidelines. Floyd Bloom, in his presidential address at the 2003 meeting of the American Association for the Advancement of Science, noted that there were at that time 10,000 medicines, >100,000 described diseases and conditions, thousands of guidelines, and millions of rules covering various aspects of medical care delivery [16]. Since then, the number of guidelines has increased. They guide medical practice in virtually all countries and some have quasi-legal status. In response to these daunting statistics (among other things), the Institute of Medicine sought to help society know what works in medical care. One early step was to decide whether to consider costs. This is a central component of healthcare economics among most governments in the world but, in the U.S., the consideration of cost in government health policy about insurance coverage decisions is often absent, sporadic, or irrational. Because of this, the committee chose not to make recommendations

about the role of cost in evaluating the value of clinical services, focusing instead on effectiveness [17]. This Institute of Medicine report noted that guideline development in the U.S. is somewhat disorganized, resulting in gross duplication of efforts in some areas and minimal efforts in others. At the time when the committee was deliberating (2006–2008), the National Guideline Clearinghouse of AHCPR received guidelines from >350 organizations. This clearinghouse contained >450 guidelines related to high blood pressure and >250 related to stroke—but few related to patient surveillance after curative-intent therapy for cancer patients, for example [18]. In contrast, in the United Kingdom (where considerations of cost are explicit), a single entity, the National Institute for Health and Clinical Excellence (NICE), is charged with generating clinical guidelines and providing guidance about public health issues, including health technologies for the National Health Service in England, Northern Ireland, and Wales. A similar entity creates separate guidelines for Scotland [19]. In the opinions of the authors of this chapter, these systems are the best of their kind in the world. However, they have produced few guidelines about surveillance for patients after initial therapy for most types of cancer.

The process of guideline development was reassessed by the Institute of Medicine in 2011 [20]. The committee concluded that trustworthy guidelines should be based on a systematic review of existing evidence; be developed by a knowledgeable, multidisciplinary group of experts and representatives from key affected groups; consider important patient subgroups and patient preferences, as appropriate; be based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest; provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of the recommendations; and be reconsidered and revised as appropriate when important new evidence warrants modification of recommendations.

The concept of patient surveillance after cancer treatment is clearly here to stay. There are many types of cancer, many forms of treatment, and many surveillance tools. Curative-intent primary therapy can be delivered to many patients with most types of cancer. Surveillance is felt to be warranted for virtually all such patients, even those in whom cure is not possible, but this book is primarily concerned with those treated with curative intent. In such patients, surveillance is felt by most patients and most caregivers to be valuable. It is regularly carried out, at least in wealthy countries. There have been few large, well-controlled trials of posttreatment surveillance strategies published in the relevant literature for most types of cancer at present. There are many reasons for this evidence deficit and the consequences are important for payers, physicians and other caregivers, patients, and their friends and families.

As an alternative approach, the authors of this book have attempted to collect and summarize succinctly the guidelines that have been generated by reputable professional societies, nonprofit groups, and relevant government agencies for many common cancers. To this end, we searched for guidelines generated by nine relevant professional groups, nonprofit organizations, and government agencies and also available on the internet: the National Comprehensive Cancer Network (NCCN, www.nccn.org), the American Society of Clinical Oncology (ASCO, www.asco.org), the European Society for Medical Oncology (ESMO, www.esmo.org), the European Society of Surgical Oncology (ESSO, www.essoweb.org), the National Institute for Health and Clinical Excellence (NICE, www.nice.org.uk) of the United Kingdom, the National Guideline Clearinghouse (NGC, www.guideline.gov), the Cochrane Collaboration (TCC, www.cochrane.org), the Society of Surgical Oncology (SSO, www.surgonc.org), and Cancer Care Ontario (CCO, www.cancercare.on.ca) in 2007–2008 and 2011–2012. Evaluation of the two searches revealed that there are few guidelines from these sources that even make specific recommendations about how frequently the available surveillance modalities (office visit, blood tests, imaging studies, etc.) should be recommended. In addition, there have been few changes between the two sets of guidelines, indicating that little new evidence has been introduced concerning patient surveillance over this period. Many clinicians refer to the NCCN guidelines when inquiring about posttreatment follow-up recommendations for their patients, in large part, apparently, because they make fairly specific recommendations.

We recognized the lack of high-quality data on this topic about 20 years ago, the subsequent vagueness of most guidelines and the weakness of the evidence base underpinning NCCN and ESMO guidelines. We set out to determine how experts around the world conduct such surveillance. The experts were all from wealthy industrial democracies and leaders in their fields. The results were published in 1995 [21]. The practices these experts recommended were often quite complex, related largely to estimated risk of recurrence. However, they were not congruent, which was not surprising in retrospect, given the minimal available evidence about the utility of any surveillance strategy and the variability among institutions, payers, treatment philosophies of the various experts, and the populations served.

We next attempted to quantify the actual practices of clinicians who treated patients with a particular form of cancer, provided posttreatment surveillance, and were members of their main professional organization. To accomplish this, we relied on custom-made survey instruments that were sent by conventional mail or email. An example is surveillance after treatment for soft-tissue sarcoma. The survey featured four brief vignettes, succinctly describing generally healthy sarcoma patients with different prognoses. It revealed dramatic

variation in the self-reported actual practice of these experts [22]. Realizing that variation is a measure of quality [23] and that unwarranted variation is prima facie evidence of overuse and/or underuse and/or misuse of scarce medical resources, we next sought to determine the source of this variation [24]. We analyzed the role of physician age in the observed variation and found that, although significant variation attributable to surgeon age was present, it was much too small to account for the overall variation previously documented [25]. We estimated the effect of the size and grade of the sarcoma on the overall surveillance variability; again significant variation was documented but it was too small to be considered a major source of the previously observed variation [26]. We evaluated the effect of the geographic location of the surgeon, which would incorporate factors such as the presence of a nearby academic center and managed care organization penetration rate. This complex analysis showed again that, though significant variability was attributable to these factors, they could not explain the overall variation we had earlier noted [27]. In an attempt to understand the motivation of the clinicians, we inquired about this directly [28]. We estimated the costs of posttreatment surveillance strategies recommended for soft-tissue sarcoma patients in an earlier textbook devoted to this topic and found 25-fold variation among the five institutions represented, based on Medicare-allowed charges [29,30]. One might presume that even greater differences among clinicians might have been detected if we had asked more experts about their strategies. Many other factors play major roles in determining surveillance intensity utilized by experts, even though we have only indirect evidence for this. Such factors include patient income, patient insurance status, patient expectations, and societal expectations. All of these differ according to the patient population served. For example, a physician caring for a cancer patient in a public safety-net hospital typically has stringent limits placed on patient-care resources. Patients who live in middle- and low-income countries, even those with national health care systems, can also be assumed to have limited resources. Even in low-income countries, of course, some citizens are wealthy and can afford excellent medical attention, often delivered in a wealthy, technologically advanced country. Failed states such as present-day Somalia are typically chaotic and basic medical care, even for simple illnesses, is often unavailable or inaccessible because of armed conflict.

Because the goals of surveillance are not well circumscribed, explicit, and generally accepted, uniformity of surveillance practice will presumably be difficult to attain. Detection of recurrence of the index cancer is a major goal in the opinions of most clinicians, followed by detection of second cancers and detection of adverse effects of treatment. Other goals are discussed in more detail elsewhere [31] but one (detection of other medically significant conditions) deserves attention here. This invites screening for hypertension and dyslipidemia, lung cancer in tobacco abusers, and the like—all of which are usually the responsibility of the patient's primary-care provider [13]. We presume that this accounts for the inclusion of tests such as liver function tests, complete blood count, urinalysis, and the like in surveillance test strategies, although they are rather unlikely to diagnose recurrent cancer, a new primary cancer, or adverse effects of initial therapy [19]. The goal of detecting other medically important conditions opens a very wide door and invites marked variability among surveillance strategies. Other likely causes of variation in surveillance strategies will be apparent to most readers of this textbook.

At present, we consider that the variation in surveillance practice for most patients after primary curative-intent therapy largely results from the belief that surveillance is worthwhile, based primarily on intuition and anecdotal evidence, the current willingness of payers in wealthy countries to pay for surveillance testing, and the lack of rigorous clinical evidence to support any particular strategy for most types of cancer.

There is some evidence derived from registry data that posttreatment surveillance can be limited in some instances. Siva et al. showed that cervix cancer patients treated with radiation and chemotherapy with a complete metabolic tumor response on posttreatment 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) were quite likely to be cured and advocated low-intensity surveillance based largely on FDG-PET scans for such patients [32]. Buchler et al. also using registry data, documented low utility of a common surveillance strategy for certain patients treated for testicular cancer and recommended that surveillance intensity should be minimal [33]. In general, patients estimated to have a very low risk of recurrence are good candidates for low-intensity surveillance. Those designing surveillance strategies should limit or abandon use of modalities with low utility.

Considering costs is rational in designing surveillance protocols. Effectiveness of testing modalities using epidemiological principles is also rational [34]. Each modality that deserves a place in a strategy in which a main goal is detection of recurrence while the recurrence is still asymptomatic can be considered a screening test. Pertinent criteria for an acceptable screening test include validity, reliability, yield, and likelihood ratios. The proposed frequency of screening using any modality that meets such criteria should probably incorporate human factors such as the preference of the doctor and the preference of the patient, although increased testing frequency could reasonably impose direct patient costs. To establish a rational screening program, consideration of the receiver operating characteristic curve, thresholds for instituting treatment, and the thresholds for testing are required (but infrequently done).

Clinicians, administrators, and other contributors in any rigorous analysis of the costs of surveillance testing must contend with limited resources and increasing demand. This reflects, to some extent, the excellence of modern diagnostic testing techniques and the excellence of modern treatment which renders so many patients free of evident cancer at the termination of initial therapy. Rigorous analysis of costs, benefits, quality, available resources, and the like is beyond the scope of this chapter but can be found in modern books about epidemiology, business, and medical care [35–47].

It should now be quite clear that devising a cost-effective strategy means one thing to the average clinician caring for a cancer patient and quite another to a health economist, insurance analyst, or technical advisor to a politician deciding whether to vote for or against a proposal to alter a national health care system. Data permitting rigorous creation of a cost-effective strategy for surveillance of cancer patients after curative-intent treatment simply do not exist in the U.S. The National Clinical Guideline Centre of the United Kingdom has created a rigorous process on behalf of NICE to develop evidence-based guidelines in which cost-effectiveness is also weighed [48]. As mentioned before, the authors of this chapter consider this process to be the best of its kind in the world at present.

The conduct of posttreatment surveillance has changed over time. A recent innovation is the patient treatment plan [49]. This is designed to enable the battery of doctors, physical therapists, and others who have been caring for a cancer patient to transfer responsibility for care to others. The plan is a written document explaining pertinent details about the patient's cancer, the initial management plan devised by the team involved in the initial work-up, diagnosis, and treatment, and elements of the treatment course that are noteworthy. The patient treatment plan informs the intended primary-care physician (and others, as appropriate) of the recommendations of the team involved in the initial care for the remainder of the patient's life. This includes such items as the schedules of diagnostic testing for recurrence of the index neoplasm and second primary neoplasms, genetic testing of relatives, as indicated, advice about appropriate management of treatment-related disabilities, and the like. The formal written treatment plan may contain a wealth of other useful information such as the contact information of those involved in primary treatment of the cancer, relevant support groups, and so on. Expected ill effects or toxicities of the treatments are often enumerated. Recommended behavioral changes (smoking cessation, avoidance of excessive sun exposure, etc.) are often included. The treatment plan has not been widely adopted, however, for practical reasons. It takes considerable effort to compile the elements and organize them in an understandable format. The physician often simply does not have enough time to create this document, so a nurse or secretary often assembles the main elements and gives the physician that draft to work with. However, lack of reimbursement is currently a major impediment. Health care systems are likely to value these plans but will presumably have to provide payment to those who create them. Computerized medical records will certainly aid in this process. The available evidence indicates that survivorship care plans are highly valued by primary-care providers [50]. They help educate these providers and influence their management of the cancer patient. However, the limited evidence to date does not suggest that such documents markedly improve patient outcomes [51].

Medical care is famously complex. It has been compared in difficulty to being a parent. The authors of this chapter feel that nihilism about the apparently illogical features of current posttreatment surveillance is unacceptable. This is why the status quo has been maintained even for medical practice guidelines that are merely based on expert consensus. The relevance of such guidelines erodes with time as new diagnostic criteria are introduced, new risk-estimation tools are devised and validated, new salvage therapies for local and distant relapse replace old therapies, and new treatments for incurable disease enter the clinical armamentarium. These considerations apply to all varieties of cancer.

The importance of posttreatment surveillance for all types of life-threatening chronic disorders (such as cancer) is underappreciated and under-researched. For example, the two large, very influential randomized trials of breast cancer surveillance [52,53] are nearly two decades old and no longer fully relevant to the practice of breast cancer management. New diagnostic modalities, new treatments for relapse, and new methods of primary breast cancer therapy are available. New trials are needed, although they are difficult and expensive to carry out. Surely patient surveillance for all forms of cancer after initial therapy deserves to be established by such trials, if feasible. Phelps and Parente have estimated that the economic returns on high-quality clinical trials exceed expenditures by one to two orders of magnitude [54]. Such trials should determine whether current guideline-compliant patient surveillance represents best medical practice.

At present, although the National Institutes of Health and other relevant funding entities consider posttreatment patient surveillance as falling within their realm [55], they do not support comparative trials of a particular surveillance strategy with an alternative strategy. The public health community has long recognized that "if we want more evidence-based practice, we need more practice-based evidence" [56]. Presumably, the community of patients, insurers, advocacy groups, health care professionals, and others will also have to advocate for adoption of enabling language in legislation to change the status quo. This is likely to be difficult. However, unless we can improve the evidence based upon which medical practice is founded, the current marked variation in practice is not likely to improve. Constraints on physician practices, based largely on cost, by medical management

systems is another potential approach to decrease such variation but one that has proven to be unpopular with physicians and patients. Such constraints, if they are not based mainly on clinical data, are likely to be sources of overuse, underuse, or misuse of resources.

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Introduction to Cancer Surveillance Strategies

2

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Keywords
Survivorship • Surveillance • Treatment • Medicolegal • Costs

Introduction

In recent decades, detection and treatment of cancer has become increasingly successful. Cure is possible and, even if it is not, therapies can lead to remission of and survival with the disease for years. In the United States alone, there are greater than 12 million cancer survivors [1]. With this number of patients experiencing what has come to be known as cancer survivorship, a need has arisen for the process of surveillance—monitoring cancer survivors for recurrence of disease. Beyond recurrence, surveillance also encompasses posttreatment complications as well as the diagnosis and treatment of secondary malignancies that can arise from initial treatment.

A patient's cancer and his or her response to treatment are unique, which leads to the question of how surveillance should be implemented. Ideally, medical practice is based on clinical and/or scientific evidence. However, this is not always feasible and, in terms of cancer survivorship, there is often insufficient evidence to generate complete surveillance strategies. Cancer societies and committees attempt to fill the void by recommending surveillance protocols based on multiple factors.

In the following chapters, guidelines for specific surveillance strategies will be outlined. Here, we attempt to explain what considerations go into choosing surveillance strategies.

First, the options for strategies have to be considered, and these vary based on the disease process. Certain cancers have specific serum markers which can be useful after treatment to detect recurrence. Imaging studies such as PET, CT, and MRI scans are available to detect metastases or local recurrence. These modalities have different sensitivities based on the cancer and organ system. Although these technologies continue to advance, the dilemma of unnecessary tissue biopsies is based on them. The primary malignancy often dictates the timing and location of recurrence and these factors should direct surveillance. If lung metastases are common, chest imaging will clearly be part of the surveillance protocol. If local recurrence is the most likely complication of the malignancy, perhaps clinical examination or local imaging is all that is needed. Delayed treatment effects and complications are a separate, but equally important, concern to the treating oncologist and patient. Lymphedema after mastectomy and axillary dissection, osteonecrosis from corticosteroids, and secondary malignancies from radiation therapy are just a few examples.

Although the prevalence of cancer survivors continues to increase, two key factors have led to a substantial lack of evidence on which to base a surveillance strategy. First of all, while standard treatment protocols are certainly in place for a majority of malignancies, individual patients continue to experience unique clinical courses based on their response. These treatment variations (i.e., whether or not a patient receives radiation, organ systems affected, chemotherapy regimens selected, and treatment complications) impact surveillance. Secondly, survivorship is still a relatively young concept and long-term data are limited. Even when evidence does exist for certain strategies, such as using prostate-specific antigen (PSA) for monitoring prostate cancer recurrence, the evidence, and therefore the recommendations, evolve as long-term follow-up becomes available. Yes, an elevated serum PSA level in a previously "cured" prostate

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