# Breast Cancer Follow-up in the Adjuvant Setting

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Breast cancer may recur through 15 years and beyond after diagnosis; thus, breast cancer patients require long-term follow-up after adjuvant treatment to detect recurrent disease. History taking, physical examination, and regular mammography are still the foundation of appropriate breast cancer follow-up in the adjuvant setting. Clearly, breast MRI has a role in certain high-risk patients, but in moderate-risk patients, the decision to use MRI must be based on the complexity of the clinical scenario. Other routine imaging studies (CT, positron emission tomography, and bone scans) and laboratory testing-including tumor marker assessments-in asymptomatic patients have not demonstrated an improvement in survival, quality of life, toxicity, or cost-effectiveness. Survivorship issues are also an inherent part of breast cancer follow-up; physicians should make every effort to address supportive care issues unique to breast cancer survivors including hot flashes, bone health, neuropathy, and risk-reduction strategies.

#### Introduction

In 2006, more than 212,000 women were diagnosed with breast cancer [1]. Despite the fact that breast cancer survival trends over the past quarter century appear to be improving [2], many patients will experience cancer recurrences in the years following definitive therapy. Useful tools such as Internet-based risk assessment calculators and gene expression profiling have been developed to assess the risk of cancer recurrence and to aid in adjuvant therapy decision-making [3,4]. Of course, no diagnostic test provides complete accuracy in predicting cancer recurrences; therefore, the goals of breast cancer follow-up in the adjuvant setting are 1) to detect loco-regional recurrences early enough to direct curative treatment, and 2) to detect distant metastases early enough to avert serious adverse events and ensure the best possible overall survival with the initiation of palliative therapy. However, in order for a surveillance test to be useful, it must positively impact survival, quality of life, toxicity, or cost-effectiveness [5].

Follow-up Guidelines and the Available Data Historically, breast cancer follow-up in the adjuvant setting has employed a conservative approach based upon clinical examination and regular breast imaging. The combination of routine history taking, physical examination, and mammography is still the most useful approach for following breast cancer patients, as reflected in the evidence-based guidelines published by the American Society of Clinical Oncology (ASCO) [6••], Health Canada's Canadian Breast Cancer Initiative [7], and the National Comprehensive Cancer Center Network [8].

ASCO published its first evidence-based clinical practice guidelines on postoperative surveillance for the detection of recurrent breast cancer in 1997, and updated the recommendations in 1998 and 2006 [6••,9,10]. Over the past 10 years, despite the development of an array of novel diagnostic tests, the guidelines have not changed substantially. A summary of the 2006 ASCO recommendations for breast cancer followup in the adjuvant setting is provided in Table 1.

The available recommendations for follow-up are consistent with the results of well-designed randomized studies [11,12] that show survival for breast cancer patients is not improved by the routine use of imaging or laboratory testing in asymptomatic women. In a Cochrane collaboration review of four randomized controlled clinical trials, Rojas et al. [13] also found no difference in survival between patients observed with intensive surveillance programs (routine bone scan, liver ultrasound, chest x-rays, and laboratory testing) and those followed with clinical visits and mammography alone. The 10-year follow-up data from the Italian National Research Council [14] of intensive versus standard breast cancer follow-up also showed no difference in survival between the two groups, despite the fact that breast cancer recurrences were found earlier in the intensive surveillance group.

Mode of surveillance	Summary of recommendations	
Recommended breast cancer s	surveillance	
History/physical examination	Examinations should occur every 3–6 months for the first 3 years after primary therapy every 6–12 months for years 4 and 5; then annually	
Patient education regarding symptoms of recurrence	Physicians should counsel patients about the symptoms of recurrence, including new lumps; bone, chest, or abdominal pain; dyspnea; or persistent headaches; helpful websites for patient education include http://www.plwc.org and http://www.cancer.org	
Referral for genetic counseling	Criteria include: Ashkenazi Jewish heritage; history of ovarian cancer at any age in the patient or any first- or second-degree relatives; any first-degree relative with a history of breast cancer diagnosed before 50 years of age; two or more first- or second-degree relatives diagnosed with breast cancer at any age; patient or relative with diagnosis of bilateral breast cancer; and history of breast cancer in a male relative	
Breast self-examination	All women should be counseled to perform monthly breast self-examinations	
Mammography	First posttreatment mammogram should occur 1 year after the initial mammogram tha leads to diagnosis but no earlier than 6 months after definitive radiation therapy; sub quent mammograms should be obtained as indicated for surveillance of abnormalitie	
Coordination of care	Continuity of care for breast cancer patients is encouraged and should be performed by a physician experienced in the surveillance of cancer patients and in breast examination, including the examination of irradiated breasts; if follow-up is transferred to a PCP, the PCP and the patient should be informed of the long-term options regarding adjuvant hormonal therapy for the particular patient; this may necessitate re-referral for oncology assessment at an interval consistent with guidelines for adjuvant hormonal therapy	
Pelvic examination	Regular gynecologic follow-up is recommended for all women; patients who receive tamoxifen should be advised to report any vaginal bleeding to their physician	
Breast cancer surveillance test	ing not recommended	
Routine blood tests	Complete blood cell counts and liver function tests are not recommended	
Imaging studies	Chest x-ray, bone scans, liver ultrasound, CT scans, FDG-PET scans, and breast MRI are not recommended	
Tumor markers	CA15-3, CA27.29, and carcinoembryonic antigen are not recommended	
FDG-PET	FDG-PET scanning is not recommended for routine breast cancer surveillance	
Breast MRI	Breast MRI is not recommended for routine breast cancer surveillance	
ASCO—American Society of Clinica PCP—primary care physician. ( <i>Adapted from</i> Khatcheressian et al.	al Oncology; CA—cancer antigen; FDG-PET—[ <sup>18</sup> F]fluorodeoxyglucose–positron emission tomography; [6••].)	

#### Table 1. Summary of 2006 ASCO guideline recommendations for breast cancer surveillance

# Current evidence-based guidelines from ASCO

Regular history taking, physical examinations, and mammography are still the foundation of appropriate breast cancer follow-up. Patients should be seen by one of their treating physicians every 3 to 6 months during the first 3 years after diagnosis, every 6 months for years 4 and 5, and yearly thereafter. During these routine visits, patients should be questioned about common symptoms of recurrence such as dyspnea, abdominal pain or swelling, bone pain, new rashes or lumps, or persistent headaches. If a new or unusual complaint arises, a directed evaluation involving pertinent imaging and laboratory assessments should be performed.

Regular mammography should also be performed. In addition to surgical changes within the treated breast, postoperative radiation therapy can cause fat necrosis, fibrosis, and other parenchymal changes in breast tissue [15]. Therefore, to allow time for some of these radiation-induced effects to resolve, the first posttreatment mammogram should not be obtained too soon after radiation therapy. For women treated with breast-conserving surgery, the first posttreatment mammogram should be performed no earlier than 6 months after definitive radiation therapy has been completed. Subsequent mammograms may be obtained more often (every 6 months) to monitor abnormalities until stability of the mammographic findings are achieved.

#### Breast self-examination

The only large study [16] of breast self-examination (BSE) evaluated its use as a screening tool in noncancer patients. The study randomized 260,000 Chinese women to BSE versus standard care; routine screening mammography was not available to the study participants. No survival difference was found between the two groups. Thus, BSE is not effective as a screening tool in the absence of routine breast

imaging for women without a prior history of breast cancer; however, its usefulness as an adjunct to mammography in the adjuvant follow-up setting is unknown.

A recent meta-analysis [17] of 12 studies involving 5045 breast cancer patients found that of those who developed symptomatic loco-regional recurrences, approximately 60% of these recurrences were found by women themselves between scheduled clinic visits. Because most breast cancer recurrences are found between regular visits, ASCO still recommends that providers counsel women on how to perform monthly BSE after definitive breast cancer treatment.

#### Variations in practice

Variations in practice patterns exist and have significant cost implications. At Centre Regional Leon Berard, Mille et al. [18] studied the impact of clinical practice guidelines on follow-up of patients with localized breast cancer. Care that was not guideline compliant cost 2.2 to 3.6 times more than guideline-compliant follow-up due to nonmammographic examinations performed in the absence of any warning signs or symptoms of recurrence. After the introduction of surveillance guidelines in 1994, there was a one-third decrease in expenditures per patient, with no change in health outcomes expected. Patients also appeared to understand the limitations of diagnostic tests and accepted limited testing from their physicians when recommended [19,20]. However, significant variation in nonrecommended follow-up testing by cancer specialists, such as tumor marker assessments and routine nonmammographic imaging, still exists [21•].

# Alternative Follow-up Strategies The role of nononcologists

Can nononcologists provide follow-up for breast cancer patients as well as oncologists? Two well-designed studies (one in Great Britain and one in Canada) have addressed this issue. In Great Britain, one randomized trial [19] involved 296 women who received followup for breast cancer in specialist oncology and surgical clinics. Patients were randomized to continued specialist follow-up (control group) or to follow-up with their own general practitioner. This study found that primary care follow-up of women treated for early-stage breast cancer is not associated with an increase in time to diagnosis of recurrence, increase in anxiety, or deterioration in healthrelated quality of life. Furthermore, it found that 69% of breast cancer recurrences presented between follow-up visits and almost half of the recurrences in the specialist group presented first to the general practitioner. In Canada, another study involving 968 early-stage breast cancer patients who were followed for a median of 4.5 years from diagnosis demonstrated the same results as the study in Great Britain [22••]. It also found that follow-up by a primary care physician (PCP) led to the same health outcomes as measured by the rate of recurrence-related serious clinical events and quality of life.

Would PCPs offer up-to-date ongoing care, such as extended adjuvant endocrine therapy, or be comfortable with many of the supportive care issues unique to breast cancer patients, such as treatment-induced hot flashes, vaginal atrophy, bone health, and neuropathy, among others? There are no studies that address this issue. Thus, it should be reassuring to patients to know that their PCPs may be able to play a role in surveillance of cancer recurrence if concurrent issues make follow-up by an oncologist prohibitively inconvenient. However, interval follow-up with an oncologist—perhaps through a shared care model—would be necessary to ensure that ongoing treatment is consistent with the current standards.

#### Less frequent and less intensive follow-up

No studies have shown that follow-up every 3 to 6 months is more effective than less frequent follow-up schedules in terms of survival or quality of life. Less frequent follow-up may also be more cost-effective and is certainly acceptable to a large number of patients; however, because all the available studies are underpowered, conclusions about the safety of less frequent follow-up visits cannot be drawn [23,24].

When given a choice, many patients will choose standard follow-up rather than more intensive follow-up strategies. A very recent study by Bornhak et al. [25•] evaluated standard follow-up (regular history, physical examinations, and mammography) versus intensive surveillance (standard follow-up plus regular chest x-rays, liver ultrasound, and laboratory work including complete blood count, carcinoembryonic antigen [CEA], and cancer antigen [CA] 15-3) in a nonrandomized fashion in 670 women with early-stage breast cancer. Patients were enrolled between 1995 and 2000 and allowed to choose their follow-up strategy; interestingly, more than 63% of participants chose the less intensive follow-up arm. After 5 years of follow-up, overall survival and relapse-free survival in the standard surveillance group were found to be noninferior to the intensive follow-up group.

# Evidence for Newer Testing MRI of the breast

Two recent studies of breast MRI screening in patients at high familial risk for breast cancer are of interest. A cohort study [26] of 529 women at high risk for breast cancer based on family history found that MRI offered higher sensitivity than mammography (91% vs 33%, respectively) at detecting breast cancer while specificity was similar (97.2% vs 96.8%, respectively). Another cohort study [27] in Great Britain of 649 women at high familial risk for breast cancer demonstrated similar results in sensitivity (MRI 77%, 95% CI, 60–90; mammography 40%, 95% CI, 24–58), but found that specificity was slightly less for MRI compared with mammography for detecting breast cancer (MRI 81%, 95% CI, 80–83; mammography 93%, [95% CI, 92–95).

A study [28••] of 969 women with newly diagnosed breast cancer with no evidence of contralateral breast cancer by mammography or clinical examination found that MRI detected occult breast cancer in the contralateral breast in 30 patients (3.1%). Ninety-one women with positive MRI findings had benign lesions on biopsy; therefore, routine breast MRI surveillance may expose patients to additional biopsies for benign lesions.

While breast MRI screening appears to be more sensitive than conventional imaging at detecting breast cancer in high-risk women, there is no evidence that breast MRI improves outcomes when it is used along with conventional breast imaging as a surveillance tool in asymptomatic patients. Earlier this year, the American Cancer Society Breast Cancer Advisory Group updated its guidelines for breast MRI screening as an adjunct to mammography [29]. The guidelines recommend MRI screening for women with a 20% to 25% or greater lifetime risk of breast cancer based on known BRCA mutation, being a first-degree relative of a BRCA carrier, or high-risk profile defined by BRCAPRO (or other family history-based risk calculators). A personal history of breast cancer alone was felt to be insufficient to recommend for or against screening. Thus, the decision to use breast MRI in women with a history of breast cancer should be made on an individual basis depending upon the specifics of the clinical scenario, such as very young age at diagnosis or extremely dense breast tissue on mammography [29].

#### **FDG-PET** scanning

The available data on [<sup>18</sup>F]fluorodeoxyglucose–positron emission tomography (FDG-PET) scanning in breast cancer surveillance come from retrospective cohort studies; there are no prospective, randomized trials. One cohort study of 61 patients compared FDG-PET scanning to conventional imaging for detecting residual or recurrent breast cancer [30]. Sensitivity of FDG-PET versus conventional imaging was slightly improved (93% vs 79%, respectively; P < 0.05), but there was no difference in positive predictive value or specificity. The negative predictive value of FDG-PET compared with conventional imaging was also improved (84% vs 59%; P < 0.05), but the impact of these results on survival, quality of life, and cost were not evaluated.

Another study [31] evaluated the efficacy of whole body FDG-PET scanning in 60 women with clinical or radiographic suspicion of recurrent breast cancer; 40 women had histologically proven relapsed disease. FDG-PET scanning was sensitive and specific for loco-regional and distant relapse and appeared to be more sensitive than tumor marker CA15-3 for detecting recurrence. However, patients enrolled in this nonrandomized study already had evidence of recurrence; therefore, no conclusions can be drawn with regard to survival or other benefits from FDG-PET scanning. A meta-analysis [32] of 16 studies comprising 808 patients demonstrated a median sensitivity and specificity of 92.7% and 81.6%, respectively, for FDG-PET scanning. The pooled sensitivity was 90% (95% CI, 86.8–93.2) and the pooled false–positive rate was 11% (95% CI, 86.0–90.6). Thus, while FDG-PET scanning appears to be a useful tool to diagnose suspected breast cancer recurrence, there are no data to support its role in routine breast cancer surveillance in asymptomatic patients, and no prospective studies have demonstrated an impact on survival, quality of life, or cost-effectiveness in the adjuvant follow-up setting.

# What Does Not Improve Outcomes? CT

One study [33] retrospectively evaluated 6628 CT scans of the pelvis in 2426 patients with breast cancer over a 9-year period. The pelvis was the only site of metastases in 13 (0.5%) patients, but these metastases led to more than 200 additional radiographic examinations and 50 surgical procedures; 84% of the additional procedures (radiographic and surgical) yielded benign or negative results. Another retrospective study [34] evaluated 250 patients with early-stage breast cancer over a 2-year period. All patients had chest radiographs (74%) or CT scans (26%) for screening purposes or to evaluate symptoms. Of the 10 (4%) patients that developed metastatic disease, only two (0.8%) had metastatic disease diagnosed by chest radiograph. No patients were found to have metastatic disease by routine chest CT scanning. There have been no other published studies that demonstrate an improvement in survival, quality of life, toxicity, or cost-effectiveness with the routine use of CT scans in the adjuvant follow-up setting.

#### CA27.29

Gion et al. [35] have demonstrated that CA27.29 is as good as CA15.3 in clinical practice, but not better. CA27.29 has been shown to detect cancer recurrences 5.3 months sooner than symptom development alone [36]. However, metastatic recurrences are incurable, and the routine use of CA27.29 has never been shown to lead to improved survival, quality of life, cost-effectiveness, or reduced toxicity. Furthermore, CA15.3 and CA27.29 rarely detect curable in-breast or loco-regional recurrences. Providers, mainly medical oncologists, continue to routinely use this test in asymptomatic patients [21•], suggesting that oncologists simply do not know the evidence against its use or do not agree with it.

#### Survivorship Issues

Follow-up of breast cancer patients in the adjuvant setting is inseparable from breast cancer survivorship. While the risk of breast cancer recurrence is highest in the first 5 years after diagnosis, cumulative breast cancer recurrences between years 5 and 15 are equal to or greater than the number of recurrences in years 1 to 5 (33.2% recurrence at 15 years vs 15.1% recurrences at year 5 in estrogen receptor-positive or estrogen receptor-unknown women treated with 5 years of tamoxifen) [37••]. Thus, for most breast cancer patients, long-term follow-up is necessary because of the heterogeneous natural history of breast cancer and the delayed recurrences that can be seen. Furthermore, breast cancer patients have a number of other concurrent issues related to their diagnosis and treatment, such as hot flashes, bone health, and neuropathy among many others; and while the quality of cancer care in the United States is excellent, there are still a number of deficiencies in how physicians approach survivorship issues [38••].

# Suboptimal survivorship care

A number of disparities in follow-up care exist. For example, African American women and women from rural areas (vs metropolitan areas) are less likely to receive regular surveillance mammography [39]. In a study of Medicare enrollees [40], more than one half of breast cancer survivors received yearly mammography 3 years after diagnosis; African American women were less likely than other women to undergo surveillance mammography. In addition, breast cancer patients report lower satisfaction with the information they receive about psychosocial needs and long-term physical effects of treatment [41]. These unmet supportive care needs are significant in the early years after diagnosis and have been reported by breast cancer patients and spouses alike [42]. Furthermore, ongoing supportive care interventions may still be needed up to 10 years after diagnosis [43]. Clearly, a significant gap exists in communication between patients and providers.

#### Underdiagnosis of symptoms

Many studies demonstrate that supportive care is suboptimal and that provider perceptions and treatment practices are often not aligned with patients' needs in such areas as anxiety/depression, neuropathy, hot flashes, and bone health maintenance [44-47]. The prevalence of anxiety and/or depression in early-stage breast cancer patients is as high as 40% [48], but oncologists often underdiagnose depression or the severity of depression [44,49]. Chemotherapy-induced neuropathy is also underdiagnosed. In a study of 300 breast cancer patients [45] receiving adjuvant taxane-based chemotherapy, providerbased neuropathy assessments, by the National Cancer Institute's Common Toxicity Criteria, underestimated the incidence and severity of chemotherapy-induced neurotoxicity (correlation with functional assessment of cancer therapy-neurotoxicity [FACT-Ntx] scale, r = 0.43) compared with patient-based assessments (correlation with FACT-Ntx scale, r = 0.70). These deficiencies also

extend to general treatment-related symptoms affecting quality of life. An observational study [50] in an outpatient palliative chemotherapy clinic revealed that in up to 54% of consultations in which patients were experiencing serious health-related quality-of-life problems, no time was devoted to discussing quality-of-life issues; emotional functioning and fatigue were not addressed 54% and 48% of the time, respectively.

#### Undertreatment of symptoms

In a cross-sectional survey [46] of 200 women treated for breast cancer, only 21% of women experiencing hot flashes were receiving any treatment for these symptoms; in addition, most women described no knowledge or poor knowledge of supportive care treatment options. A retrospective cross-sectional survey [47] of 102 breast cancer patients with chemotherapy-induced menopause showed that only 56% of patients reported discussing bone health or calcium supplementation with their physicians and only 40% reported having bone mineral density testing recommended.

Can patient involvement improve the quality of supportive care in areas such as dyspareunia, chronic pain or neuropathy, anxiety, and depression among others? Unfortunately, physicians are often unaware of the desire of patients to have a shared role in decision-making [51,52]. All this emphasizes the need for improved efforts at honest communication and patient education during follow-up care.

#### Other risk-reduction strategies

Do oncologists discuss the importance of exercise [53], dietary fat reduction [54•], or vegetable and fruit intake [55] in reducing breast cancer recurrence? In a welldesigned, prospective study [54•], 2437 women with early-stage breast cancer were randomized to a low-fat diet (~ 30 g of fat/d) versus control. After a median follow-up of 60 months, recurrences were seen in 9.8% of women in the dietary group versus 12.4% in the control group. The hazard ratio of relapse events in the intervention group compared with the control group was 0.76 (95% CI, 0.60–0.98; P = 0.077 for stratified log rank and P = 0.034 for adjusted Cox model analysis). There was also a modest but statistically significant (P = 0.005) weight difference of about 6 lbs between groups, with dietary intervention women weighing less through 5 years of observation. Subset analysis indicated a stronger effect of dietary intervention in women with hormone receptor-negative cancers, but additional study is needed to confirm those findings.

Moderate physical activity may also reduce the risk of breast cancer recurrence. In a prospective, observational study of 2987 registered nurses [53] diagnosed with stage I–III breast cancer, the adjusted relative risk of death from breast cancer was 0.50 (95% CI, 0.31–0.82) for women who performed the equivalent

Patient Name:	medica	I record number:
Date of diagnosis:		
My professional society h	nas made the following reco ommend routine blood wor	ommendations for women in your k, x-rays, or ultrasounds:
<b>A careful history and exa</b> for years 4–5, then annua		ears 1–3, every 6–12 months
Monthly breast self-exam	<b>n:</b> Would you like instruction	ons? Yes No
Yearly mammogram (mo your next mammogram is		<b>lvic exam and PAP smear (Annually)</b> our next exam is due
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of walking 3 to 5 hours per week at an average pace. Interestingly, there was little evidence of a greater benefit from even higher levels of physical activity. Another prospective study [55] in 1490 early-stage breast cancer patients assessed for dietary patterns and physical activity found an approximately 50% reduction in risk of death associated with healthy lifestyle behaviors. In a multivariate Cox model, the combination of consuming five or more daily servings of vegetables or fruits and performing the equivalent of walking 30 minutes per day was associated with a significant survival advantage (HR 0.56, 95% CI, 0.31–0.98). Interestingly, this risk reduction was observed in obese and nonobese patients; unfortunately, only a minority of patients followed these healthy lifestyle patterns. How well do oncologists address these risk-reduction strategies for early-stage breast cancer patients? Very little data are available on how often this is done; given the time constraints faced by most oncologists, these issues are likely to be overlooked in a busy practice.

## Long-term Implications

An ASCO-commissioned study estimates that by 2020 the demand for oncology services will grow by 48%, but the services available will grow by only 14% (http:// www.asco.org/workforce) [56•]. Who will provide all the breast cancer follow-up care that will be needed in the next 15 to 20 years? We know that in certain populations of breast cancer patients, the rate of annual

mammography declines within a few years after diagnosis [40,57]. Will disparities in cancer care delivery only be exacerbated with a shortage of oncologists? Will the shortage increase the role of PCPs in breast cancer surveillance since follow-up by PCPs appears to lead to the same health outcomes as specialist follow-up  $[22 \bullet \bullet]$ ? Will PCPs be aware of the latest data on extended endocrine therapy, supportive care strategies, and other survivorship issues? Perhaps patients will take on a more active role in their breast cancer survivorship by participating in a shared decision-making model of care. This may necessitate the use of information technologies such as portable health records or online information sites that detail common supportive care needs and suggested interventions. Further study is required to address these important issues.

At the Virginia Commonwealth University/Massey Cancer Center, we present our follow-up patients with a breast cancer survivorship sheet (Fig. 1), in addition to a copy of the ASCO guidelines, that details upcoming provider appointment dates, date of next mammogram, and helpful websites for further information. It also provides a supportive care section about risk-reduction strategies and encourages patients to mention any specific symptoms (eg, hot flashes) or concerns (eg, familial risks). In this way, we hope to foster a more interactive approach to breast cancer survivorship for those patients interested in taking an active role in their own care.

# Conclusions

The foundation of appropriate breast cancer followup in the adjuvant setting is straightforward; it simply requires regular history taking, physical examinations, and regular mammography. Long-term follow-up for survivors is needed because breast cancer may recur 15 years and beyond after diagnosis. Clearly, there is a role for breast MRI in certain high-risk patients, but in moderate-risk patients, physicians should apply their best judgment to the particular clinical situation. Other routine imaging studies (CT, PET, and bone scans) and laboratory testing, including tumor marker assessments, in asymptomatic patients have not demonstrated an improvement in survival, quality of life, toxicity, or cost-effectiveness. Finally, survivorship issues are an inherent part of breast cancer follow-up as well; physicians should make every effort to address supportive care issues unique to breast cancer survivors including hot flashes, bone health, neuropathy, and riskreduction strategies.

# Disclosures

No potential conflicts of interest relevant to this article were reported.

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