



Challenges in Implementing Optimal Echocardiographic Screening in Cardio-Oncology

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Abstract

Purpose of review Echocardiography is the foundation of noninvasive screening in patients exposed to potentially cardiotoxic chemotherapeutic agents. Guidelines are becoming more consistent in regard to screening and recommend an integrative approach between cardiology and oncology providers as well as optimal non-invasive imaging modalities. Optimal screening with the latest technology will place a significant cost and administrative burden on echocardiographic laboratories and cardiology clinics.

Recent findings This review seeks to explore the latest studies regarding quality, cost, patient burden, and value related to implementing wide-spread screening for patients exposed to cardiotoxic chemotherapy. 3D and speckle tracking echocardiography are more reliable and can detect more subtle changes than traditional 2D volumes. Limited studies have revealed an uptake of optimal screening between 30 and 40%. Even fewer studies have evaluated the system-wide cost and value impact of screening in cardio-oncology or have evaluated patient-centered outcomes, such as cost and time burden. Finally, novel approaches, such as the use of point of care ultrasound with artificial intelligence guidance, may help alleviate these challenges.

Summary Screening patients at risk for cancer therapeutics-related cardiac dysfunction poses real-world challenges to our healthcare system. While modern echocardiographic techniques improve our ability to detect cardiac dysfunction, further research is needed to understand the challenges of wide-spread implementation.

Introduction

Advances in both detection and treatment options have led to increased survival in patients diagnosed with cancer [1]. However, some of these therapies are directly cardiotoxic and the impact of cardiovascular health in cancer survivors is an active area of investigation. Echocardiography is the most commonly used modality in diagnosing and monitoring cancer patients for cardiotoxicity. The specific techniques and real-world use of echocardiography are constantly changing as new data emerge and practice patterns change. Guidelines are evolving and are gradually becoming more consistent and evidence based. Yet, as the use of echocardiography expands and newer techniques become available, cost, value, and accessibility become relevant issues. In this review, we seek to establish the current role of echocardiography in cardio-oncology, current issues the field is facing, and potential solutions to provide high-quality care to a wide group of patients.

Definition of cardiotoxicity

A formal definition of cardiotoxicity caused by cancer-related therapeutics was provided by the ASE and EACI consensus statement in 2014 as a decrease in LVEF of greater than 10 percentage points to a value of less than 53%, of which should be confirmed by repeated cardiac imaging 2 to 3 weeks after the original baseline study [2]. Important features to be considered throughout this evaluation include whether the decrease in left ventricular ejection fraction (LVEF) is associated with any change in clinical symptoms, such as dyspnea on exertion. Cancer therapeutics-related cardiac dysfunction (CTRCD) has been classically associated with radiation therapy and drugs such as anthracyclines and HER2 receptor blockers which in themselves cause different mechanisms of toxicity.

Cardiotoxic therapies

Anthracyclines (doxorubicin, daunorubicin) are chemotherapy drugs that have been instrumental in the treatment of solid, as well as hematologic malignancies [3]. Cardiotoxicity from these agents is a dose-limiting process, but damage at a cellular level can be seen with the current relatively low-dose administration protocols [4]. This mechanism of injury was classically thought to cause irreversible myocardial injury via cell death, but with the discovery of new chemotherapy agents causing

cardiotoxicity, our understanding of exact mechanisms has been challenged [2].

Trastuzumab is a monoclonal antibody approved for the treatment of metastatic breast cancer that overexpresses a proto-oncogene encoded by the HER2 gene. Trastuzumab in contrast to anthracyclines does not cause dose-dependent damage [2]. It has been found that CTRCD associated with trastuzumab use has the potential to be reversible, with reported rates of improvement with medical management and cessation of drug to be 79% [5]. Prior use of anthracyclines reduces the likelihood of reversibility in patients subsequently treated with trastuzumab, which is thought to be secondary to the elimination of cardiac reserve needed to compensate [6]. The differentiation between these types of injury is not as clearly delineated in real life, with the timeline of cardiotoxic injury, and baseline risk factors prior to cardiac therapy influencing reversibility.

With the expansion of the molecular approach to the treatment of cancer, new mechanisms of cardiotoxicity have emerged in the last two decades. Agents such as tyrosine kinases inhibitors, vascular endothelial growth factor (VEGF) pathway inhibitors, proteasome inhibitors, immune checkpoint inhibitors including PD-1 (programmed cell death protein 1), PD-L1 (PD ligand 1), and CTLA-4 (cytotoxic T cell lymphocyte-associated protein 4) inhibitors have all been proposed to cause some degree of cardiotoxicity by varying mechanisms [7, 8]. However, unlike anthracyclines and HER2 blockers, there are no established guidelines on how to monitor the downstream effects of these therapies.

Guidelines for surveillance protocols

Prior to initiating any potentially cardiotoxic chemotherapy regimen, a thorough evaluation including physical examination, medical history, identification of cardiac risk factors, and baseline assessment of left ventricular function should be pursued according to institutional standards. This initial approach can stratify patients who would otherwise be at risk for CTRCD.

Multiple professional societies in the fields of both cardiology and oncology have released consensus statements regarding the approach to management of these patients at risk for the development of CTRCD (Table 1). These consensus statements include proposed algorithms for surveillance imaging of patients undergoing cardiotoxic chemotherapy and actively managing modifiable risk factors such as smoking, hypertension,

hyperlipidemia, obesity, and diabetes [9•]. By identifying high-risk patients early, providers have the opportunity to treat/pre-treat with cardiac medications, conduct routine assessments of cardiac function and can advise whether or not dose reduction in cancer therapies is needed. Characteristics of high-risk patients include age > 65, prior LV dysfunction, risk factors for cardiovascular disease, treatment plan consisting of high-dose agents, and combination cardiotoxic therapies [2]. While the role of imaging is discussed, the ASCO guidelines highlight how important the role of the clinician is for predicting, preventing, and diagnosing CTRCD.

More recently, the American Heart Association released a statement outlining the scope of cardiovascular disease in patients with breast cancer [10•]. Like other institutional guidelines, this study acknowledged that assessment of LVEF obtained by echocardiography is a reasonable first step to identify patients with CTRCD. However, significant changes in ejection fraction discovered by echocardiography may be a late manifestation of extensive cardiac damage, creating the need for more sensitive modalities to detect early cardiac dysfunction. One proposed solution is combining myocardial strain imaging with the presence of elevations in cardiac biomarkers [10•]. Sawaya et al. found that the combination of a 10% relative decrease in global longitudinal strain imaging (GLS) with elevated troponin I levels had higher specificity for predicting cardiotoxicity than either alone [10•, 11].

Common themes in these treatment guidelines are recommendations to obtain a baseline assessment of cardiac structure and function around the initiation of potentially cardiotoxic medications—regardless of mechanism of CTRCD. Identifying and treating modifiable risk factors can help mitigate the effects of cardiotoxic chemotherapy regimens. The preferred initial imaging modality is 3D echocardiography, and if 2D echocardiography is the only available modality, it is recommended to use contrast to enhance endocardial border definition and thus reliability. Myocardial strain imaging is a newly established modality and has been identified as a more sensitive tool in detecting subclinical changes in left ventricular function.

Limitations of these proposed surveillance guidelines are mostly related to the inherent limitations of the imaging modalities used to evaluate left ventricular function. For example, measuring ejection fraction via 2D echocardiography has been shown to demonstrate temporal variability which makes EF trends difficult to interpret [12]. These guidelines additionally lack a

strong consensus on the utilization of resources, particularly in the use of more advanced techniques that may not be widely available. Furthermore, there is a lack of recommendations regarding the role of treatment teams and non-physician providers to actively monitor for signs of CTRCD separate from scheduled yearly or bi-yearly echocardiograms.

Uptake of guidelines

Relatively few studies have looked at the real-world adequacy of cardiac monitoring in these patient populations. This information is crucial, as advances in cancer therapy and survival will inevitably result in providers seeing more patients with adverse cardiovascular outcomes who will require optimal surveillance. A study by Chavez-MacGregor et al. used the Surveillance, Epidemiology, and End Results (SEER) Medicare and Texas Cancer Registry to identify 2203 patients age ≥ 66 who were diagnosed with invasive breast cancer stage I to III between 2005 and 2009. Adequate cardiac monitoring was defined as having a baseline echocardiogram (or MUGA scan) within 4 months of the first dose of chemotherapy with subsequent follow-up at least every 4 months while receiving trastuzumab. Results of this study demonstrated that baseline cardiac evaluation was performed in 78.8% of patients. A 4-month follow-up evaluation after receiving trastuzumab was performed in 68.2% of the patients. Furthermore, only 42.6% of patients had cardiac evaluations every 4 months according to their definition of adequate cardiac monitoring. In total, only 36% of patients had adequate cardiac monitoring according to the study's predetermined guideline. Thus, patients with breast cancer were receiving suboptimal cardiac monitoring while undergoing cardiotoxic chemotherapy treatment [13].

The same group published another study in 2018 further examining adherence to cardiac monitoring among breast cancer patients receiving chemotherapy. A similar schedule as the above study was used to determine adequate cardiac monitoring using a baseline cardiac evaluation and subsequent 4-month serial echocardiograms. A larger cohort of patients was examined (4325) and rates of cardiac monitoring were examined by age groups within the MarketScan database. Results found that 79.5% of patients less than 35 years of age received baseline cardiac monitoring compared to 86.1% of patients 65 years or older. Furthermore,

Table 1. Expert consensus surveillance algorithms

Professional group	Baseline EF measurement before therapy	During anthracycline therapy	After anthracycline therapy	After anthracycline therapy	After HER2 targeted therapy	GLS
American Society of Echocardiography/-European Association of Cardiovascular Imaging 2014 [2]	Yes	If total anthracycline dose is >240 mg/m ² , cardiac monitoring should be performed before every additional 50 mg/m ² .	Every 3 months during treatment	At completion of therapy and 6 months later in those with total anthracycline dose of <240 mg/m ²	No routine testing if asymptomatic	If obtained during routine surveillance, cardiology consultation is recommended if GLS is <LLN according to vendor, gender, and age.
American Society of Clinical Oncology 2017 [9•]	Yes (only if symptoms concerning for cardiac dysfunction are present during routine clinical assessment)	Routine surveillance imaging may be offered during treatment in asymptomatic patients considered to be at increased risk of developing cardiac dysfunction	Clinicians may use routine echocardiographic surveillance in patients receiving trastuzumab indefinitely. The frequency of cardiac imaging for each patient to be determined by health care providers based on clinical judgment and patient circumstances.	Asymptomatic patients with a presumed elevated risk of potentially developing LV dysfunction may undergo imaging 6 to 12 months after completion of cancer therapy	Asymptomatic patients with a presumed elevated risk of potentially developing LV dysfunction may undergo imaging 6 to 12 months after completion of cancer therapy	No specific recommendations

40.2% patients less than 35 years of age received the recommended cardiac monitoring schedule laid out by this group, whereas 45.5% of individuals with age greater than 65 adhered to the recommended monitoring schedule [14•]. The limited available data suggests that far less than half of patients are receiving optimal surveillance.

Diagnostic modalities

Traditionally, 2D echocardiography (2DE) is the most commonly used imaging modality in the initial evaluation and subsequent detection of cardiotoxicity from chemotherapy regimens. 2DE is widely available, inexpensive, and has well-established techniques in the assessment of LV systolic function [15] (Table 2). Unlike multigated acquisition scanning (MUGA), 2DE is free from ionizing radiation and hence is a more benign diagnostic modality—allowing serial imaging to pose little risk to the patient. Although cardiac magnetic resonance imaging (CMRI) is the gold standard in the assessment of left ventricular function, 2DE is more widely accessible. Assessment of LVEF is most commonly performed by Simpson's biplane method of disks [15]. However, there are limitations to this method including LV geometric assumptions, foreshortening of the LV apex, and difficulty in the assessment of endocardial borders (16). When inadequate visualization of endocardial borders is present, the use of echocardiography contrast has been shown to correlate better than non-enhanced measurements [17]. However, the use of 2DE in the assessment of LVEF has significant temporal variability and has been shown to only be reliable in the detection of changes as much as 10% in serial measurements [12]. This 10% difference is not negligible, as this is within the same threshold that determines whether or not CTRCD is present [2]. The use of micro-bubble ultrasound contrast can improve endocardial definition but has several practical limitations. Contrast requires placement of an intravenous catheter as well as careful administration and knowledge of vendor's contrast package. Furthermore, with black-box warnings on the last generation of agents, administrative barriers may exist for rapid and seamless integration of contrast agents into workflow. Fortunately, the latest generation of agents are free of black box warnings, are easier to administer, and may be practical for widespread use.

The use of 3D echocardiography (3DE) overcomes some of the limitations of 2DE and is the preferred initial imaging modality in the assessment of CTRCD when available [2]. Not only does 3DE overcome the

geometrical assumptions of 2DE by capturing the entire volume of the LV during image acquisition [27], but it also has better intra- and inter-observer variability in sequential measurements in experimental conditions [18]. 3DE has its own limitations including the need for high-quality images, operator experience, and may not be widely available due to workflow limitations [2]. The need for high-quality images stems from the way these 3D images are obtained. Software packages apply a 16 segment derived model onto the LV structure and an algorithm subsequently tracks the endocardial border throughout the cardiac cycle and creates regional volume curves and EFs that can be determined for each myocardial segment [19]. Thus, having quality images with clearly defined endocardial borders is crucial for accurate results. Although automated software is becoming more common place, operator experience still plays a role in obtaining 3D data and the extensive user input can affect workflow in busy laboratories [20]. Despite these limitations, 3DE has been noted to be the imaging modality of choice in monitoring the effects of cardiotoxic chemotherapy and has the capability to detect changes in LV function down to 5–6% [12, 28].

It has been postulated that changes in EF could be a late manifestation of underlying myocardial damage. Global longitudinal strain (GLS) using speckle tracking echocardiography (STE) is a newer imaging modality that aims to detect subclinical changes in cardiac function that can precede changes in ejection fraction [29]. This technique measures regional myocardial deformation by tracking ultrasound targets within the myocardium [30]. GLS imaging has excellent specificity and sensitivity and low intra and inter-observer variability [21, 22]. However, unlike cardiac volumes and ejection fraction, there is no verifiable gold standard for echo-derived strain. Some studies have used CMRI as a standard and found correlations, but the techniques are different and may generate different results. To compensate for this, more recent studies are using a relative decline in strain, rather than a set point. These studies have shown that a 10–15% reduction in absolute GLS using STE has been shown to predict the development of future cardiotoxicity [21, 23]. Multiple studies have demonstrated that GLS reduction often precedes LVEF reduction, but this may in part be due to better reproducibility [31–33]. Although considered to be superior to 2DE and 3DE in the assessment of subclinical changes in cardiac function and the prediction of future cardiotoxicity, there are still limitations with this technique.

Table 2. Strengths and limitations of imaging modalities

Modality	Strengths	Limitations	Normal range limits	Recommendation
2D Visual	Widely available; inexpensive	Operator dependent, imprecise, inaccurate	EF >50%	Not recommended by any guideline. Method of last resort
2D Biplane	Widely available; inexpensive; has well established techniques in the assessment of LV systolic function [15]	Temporal variability; LV geometric assumptions; foreshortening of the LV apex; difficulty in the assessment of endocardial borders [12, 15–17]	EF >50%	No recommended. If other modality is not available, use of ultrasound contrast agent to enhance is recommended [17]
3D Volumes	Better intra and inter-observer variability in sequential measurements than 2DE [18]	Need for high quality images; operator experience; not widely available due to workflow limitations [19, 20]	EF >50%	Recommended imaging modality for ventricular volumes and ejection fraction [2]
GLS (Global Longitudinal Strain)	Excellent specificity and sensitivity and low intra and inter-observer variability; GLS reduction can precede changes in EP; reproducible [21–23]	Dependent on image quality; dependent on frame rate; inter-vendor variability [24–26]	–19% to –21% (varies by study and vendor) Recommended to use relative change of 10–15% decrement from baseline	Recommended if available for detect of subclinical dysfunction [2]

Like 3DE, image quality is important, and when speckle tracking is poor in more than two myocardial segments in a single view, calculation of GLS should be avoided [34]. In addition to acquiring high-quality images, maximizing frame rate enables reliable tracking of tissue velocities so that strain rate can be calculated [24]. This may be particularly problematic for echo labs using older machines or failing to optimize their images to maximize frame rate. Additionally, in everyday clinical practice, GLS results can vary dependent on which software or ultrasound machines are used by a particular laboratory. A recent study found that there is statistically significant inter-vendor variability in GLS measurements when comparing seven different ultrasound machine vendors and two software-only vendors [25, 26]. Despite these limitations, GLS has promising implications for the field of cardio-oncology and proves to be a reproducible imaging modality with earlier diagnostic and prognostic value.

GLS has been shown to be able to detect subclinical differences in systolic function, demonstrating its value as a tool in the early detection of CTRCD. This begs the question whether more widely used echocardiography parameters (2DE, 3DE) can provide reproducible data. In a key study by Thavendiranathan et al., this group compared 3DE and 2DE head to head in an attempt to determine the method of EF assessment with the lowest temporal variability [12]. The importance of this marker stems from most guidelines recommending serial echocardiograms following cardiotoxic chemotherapy, creating a need to have reliable imaging that can detect changes in left ventricular function. Their analysis was performed by selecting only patients receiving chemotherapy with stable cardiac function. This was defined as having stable GLS at five different time points (3, 6, 9, and 12 months). Stability was defined by GLS less than or equal to –16% at each time point. This was done to ensure that any changes seen in 2DE and 3DE were due

to temporal variability rather than chemotherapy-induced cardiotoxicity. Cardiac assessment using 2DE and 3DE both with and without contrast was then obtained at each time point. Ultimately, their findings demonstrated that non-contrast 3DE was found to be superior to 2DE with significantly lower temporal variability. The use of contrast only improved accuracy and reproducibility in 2DE.

While the guidelines themselves are cognizant of these limitations and make specific recommendations to improve reliability, the actual implementation may be challenging for individual practices and laboratories.

Real-world use of echo in cancer

Cost

The field of cardio-oncology is still emerging, and there is variability in the way patients are monitored for CTRCD. To date, the cost of serial cardiac imaging of patients with CTRCD has not been studied extensively. One study by Nola et al. investigated the cost effectiveness of using a strain-guided approach to managing patients with CTRCD [35]. Using GLS, this group identified high-risk patients receiving chemotherapy and initiated cardio-protection strategies such as beta blockers and ace inhibitors. Using GLS-guided therapy provided additional quality-adjusted life years (QALYs) at lesser cost compared to treating patients based on traditional LVEF-derived measures. This is significant as the current strategy of detecting CTRCD using LVEF, may identify patients who have already sustained significant cardiac damage, and therefore may not respond to cardio-protective therapies [36]. Despite the lack of data regarding the cost effectiveness of frequent cardiac monitoring, it appears that using a strain-guided approach may be a more cost-effective method.

Another study, using childhood cancer survivors as a model, aimed to determine the cost-effectiveness of routine LVEF monitoring to detect asymptomatic left ventricular function [37]. Their model including a cohort of 15-year-old cancer survivors at 30 to 35 years since diagnosis, estimated a cumulative systolic heart failure incidence of 3.6% to 5.0% [37]. Furthermore, routine cardiac imaging obtained every 10 years with 2D echocardiography (beginning 5 years after diagnosis and repeated at 10-year intervals) reduced absolute lifetime systolic CHF risk by 2.3%. Although their findings suggest that current recommendations for the frequency of

cardiac imaging may reduce the incidence of systolic heart failure, less frequent screening may be more cost effective as determined by QALYS [37]. It must be noted that incremental cost-effectiveness ratios for more frequent assessment (every 2 years) for patients exposed to ≥ 250 mg/m² of total anthracyclines were much lower than less frequent assessment (every 5 or 10 years) [37]. Thus, in childhood cancer survivors, it may be more cost effective to have less frequent screening in patients who receive low cumulative doses of chemotherapy.

Burden

In addition to systemic cost-benefit ratio, patient burden regarding time and cost must be considered when implementing wide-spread monitoring. In childhood cancer survivors, there is often a long latency period before clinically obvious cardiac dysfunction is evident [38]. Thus, it may be cost effective to reduce the frequency of cardiac monitoring early after completion of therapy in the absence of symptoms—especially in patients receiving lower doses of anthracyclines. One study found that in a cohort of patients greater than age 5 who were treated with < 250 mg/m² that none had evidence of left ventricular dysfunction after 10 years of screening. Postulating that prolonged echocardiographic screening could be reconsidered in this group which could produce a significant reduction in their burden of follow-up [39]. Other studies have similarly found that 10 years after exposure, echocardiography is not cost-effective in patients treated with less than 250 mg/m² after age 5 [37, 40]. More studies evaluating patient-related issues, such as out of pocket costs, time burden, and anxiety over test results are needed to fully understand the impact of current monitoring guidelines.

Future perspectives

Echocardiography laboratory-based speckle tracking, 3DE technology, and 2DE have become firmly implanted imaging modalities that are commonplace for the evaluation of CTRCD. However, with the improved technology of portable ultrasound units, it must be tested whether or not this technology can play a role in the screening and triage of patients undergoing cardiotoxic chemotherapy. In the outpatient setting, the current guidelines require serial echocardiograms to monitor for CTRCD as previously described. Formal echocardiogram appointments can often be time consuming for patients and require separate appointments from cardiology and oncology outpatient visits. Focused

cardiac ultrasound (FCU) is the use of portable ultrasound devices to perform a focused examination in conjunction with physical exam to recognize specific ultrasound signs that represent a narrow list of potential diagnoses in specific clinic settings [41]. With this in mind, FCU is not expected to replace formal 2DE and is not a comprehensive evaluation of cardiac structure and function. The question remains, can advanced providers of non-cardiology professions use FCU technology to help guide treatment decisions?

Raza et al. recently presented a study to determine if FCU can be used to reliably evaluate left ventricular function (LVEF) by an advanced practice provider (APP) to assess for CTRCD in Oncology patients and its impact on patient care and workflow [42]. In this study, an Oncology APP was trained on FCU and LVEF analysis using Simpson's Biplane technique on Philips Xcelera software. Their results were promising and demonstrated that FCU can potentially be used in the oncology clinic to provide a rough screen of cardiac function. Although not meant to replace formal evaluation of

potential CTRCD in the clinical setting, FCU can help identify significant changes in EF. This has the potential to reduce the cost and delay of making decisions in regards to chemotherapy dosing in busy clinical environments.

FCU methodology is an interesting juxtaposition to current practices in the field of cardio-oncology where the current trend has been to use more advanced imaging techniques to detect cardiac dysfunction. However, there are newer technologies that have been developed to help reduce operator dependency on the acquisition of quality images for FCU units. Software that has "self learning" capabilities can help determine when optimal cardiac windows have been captured by operators. Using a deep convolutional neural network model, Abdi et al. was able to provide real-time feedback to operators during image acquisition to improve image quality [43•]. This newer technology has the capability of bringing FCU to the forefront of clinical care by increasing workflow efficiency without sacrificing image quality.

Conclusions

Advances in cancer therapy and survival will inevitably result in providers seeing more patients with adverse cardiovascular outcomes. It is estimated that by 2026, the number of cancer survivors will reach more than 20 million in the USA [44•]. With this in mind, the importance of accurately identifying cardio-toxicity during chemotherapy cannot be understated. Although 2DE has been the primary method of EF assessment in the initial evaluation and subsequent detection of cardiotoxicity from chemotherapy regimens, limitations such as temporal variability and geometric assumptions have paved the way for more advanced imaging modalities. Compared to 2DE, 3DE has improved temporal variability for more accurate EF assessment in serial imaging during chemotherapy. Newer imaging modalities such as global longitudinal strain (GLS) using speckle tracking echocardiography (STE) may help to detect subclinical changes in EF, allowing providers to initiate cardio protective measures before changes in EF take place. This also may be a more cost-effective approach [35].

In regards to appropriate cardiac monitoring, research has shown that there has been suboptimal adherence to guidelines. In general, the percentage of patients undergoing baseline assessment of cardiac function before cardiotoxic chemotherapy was much higher than patients receiving serial follow-up studies. Given these statistics, does it make sense to utilize FCU to screen for cardio-toxicity in a busy clinical environment, separate from every 3-month serial cardiac function assessments? One new paradigm would be to enable non-cardiology-trained health care providers in oncology clinics to perform FCU-

based imaging protocols that assess for LV dysfunction in addition to physical exam and clinical history. Subsequently, reductions in LVEF identified via FCU could then be used to triage patients to receive more advanced imaging modalities such as GLS or 3DE. Chemotherapy regimens could also be interrupted or reduced in real time before cardiology consultation, to help mitigate cardiotoxic effects of treatment. However, more research needs to be done to assess the clinical impact and effect on workflow of this proposed system.

Compliance with Ethical Standards

Conflict of Interest

James P. McDonald and James P. MacNamara each declare no potential conflicts of interest. Vlad G. Zaha is supported by the Cancer Prevention Research Institute of Texas (CPRIT) research award RP180404.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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