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THE PRESENT AND FUTURE

COUNCIL CLINICAL PERSPECTIVES

Cardiovascular Health of Patients With Cancer and Cancer Survivors

A Roadmap to the Next Level

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ABSTRACT

Many existing and emerging cancer therapies have a significant effect on the cardiovascular health of patients with cancer and cancer survivors. This paper examines current aspects of interdisciplinary cardio-oncology clinical care delivery and education in the United States and outlines how these data provide a platform for future development of the field. We present the results of the nationwide survey on cardio-oncology services, practices, and opinions, conducted among chiefs of cardiology and program directors, which demonstrate ranges of clinical activities and identify significant interest for increased educational opportunities and expert training of cardiovascular physicians in this field. The survey respondents recognized clinical relevance but emphasized lack of national guidelines, lack of funds, and limited awareness and infrastructure as the main challenges for development and growth of cardio-oncology. We discuss potential solutions to unmet needs through interdisciplinary collaboration and the active roles of professional societies and other stakeholders. (J Am Coll Cardiol 2015;65:2739–46) © 2015 by the American College of Cardiology Foundation.

Evidence increasingly shows that cancer and heart disease are inextricably linked, whether through common risk factors, coexistence of both diseases in an aging population, or the deleterious effects of cancer treatments on cardiovascular (CV) health. Despite a growing recognition of the importance and complexity of these relationships, the vast majority of CV professionals have little

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ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

ASCO = American Society of Clinical Oncology

CV = cardiovascular

NCI = National Cancer Institute

training or exposure to the many new advances in the field of cancer therapeutics and their possible adverse CV effects. There are substantial opportunities for CV specialists to advance partnership with oncologists in exploring new strategies to preserve and restore optimal CV health of patients with cancer and cancer survivors and for CV scientists to unravel the links between these disorders.

Due to significant College-wide interest, the American College of Cardiology's (ACC's) Early Career section has developed a working group to explore the potential in developing this new focus on cardio-oncology, including a potential new member section: Cardio-Oncology. In collaboration with ACC staff, this group has performed an environmental scan and conducted a nationwide survey of cardiologists regarding their views on cardio-oncology services, practices, and opinions to identify patient and professional needs in this growing field.

The aim of this paper is to summarize the key current aspects of interdisciplinary cardio-oncology clinical care delivery and education in the United States and to outline how these data provide a platform for future development of the field. As part of the ACC's strategic mission to provide a professional home for CV specialists, we examine existing interests and expertise, as well as available forums and opportunities for education and knowledge exchange. This paper does not present a comprehensive review of the considerable clinical or research publications within cardio-oncology, but rather a snapshot of the needs and opportunities in patient care, training, and education in this field. We then discuss potential next steps to advance the field and interdisciplinary collaboration.

THE ORIGINS OF CARDIO-ONCOLOGY OR ONCO-CARDIOLOGY

The terms "cardio-oncology" and "onco-cardiology" have both been used to describe this field, encompassing a continuum of CV risk stratification, prevention, and treatment that spans the timeline from cancer diagnosis into survivorship (**Figure 1**) and that depends on close collaboration across cardiology and oncology specialties (1–3). The origins of the field date back to the late 1960s, when anthracyclines, potent new antitumor compounds, were widely introduced into the therapeutic regimens of many cancers (4–6). Observations of their dose-dependent cardiotoxic effects not only led to critical modifications of anthracycline-based regimens with cumulative dose limits (7), but also spurred research directed toward the understanding, diagnosis, and prevention of cardiac toxicity. Anthracycline-induced cardiac injury became a prototype of what later was named type I cancer therapy–related cardiac dysfunction, characterized by ultrastructural evidence of necrosis, dose dependence, and largely irreversible effects on cardiac muscle (8,9). In contrast, type II cancer therapy–related cardiac dysfunction is associated with the use of molecularly targeted cancer therapeutics, the effects of which are not dose related, do not have molecular evidence of necrosis, and are often reversible (8,9).

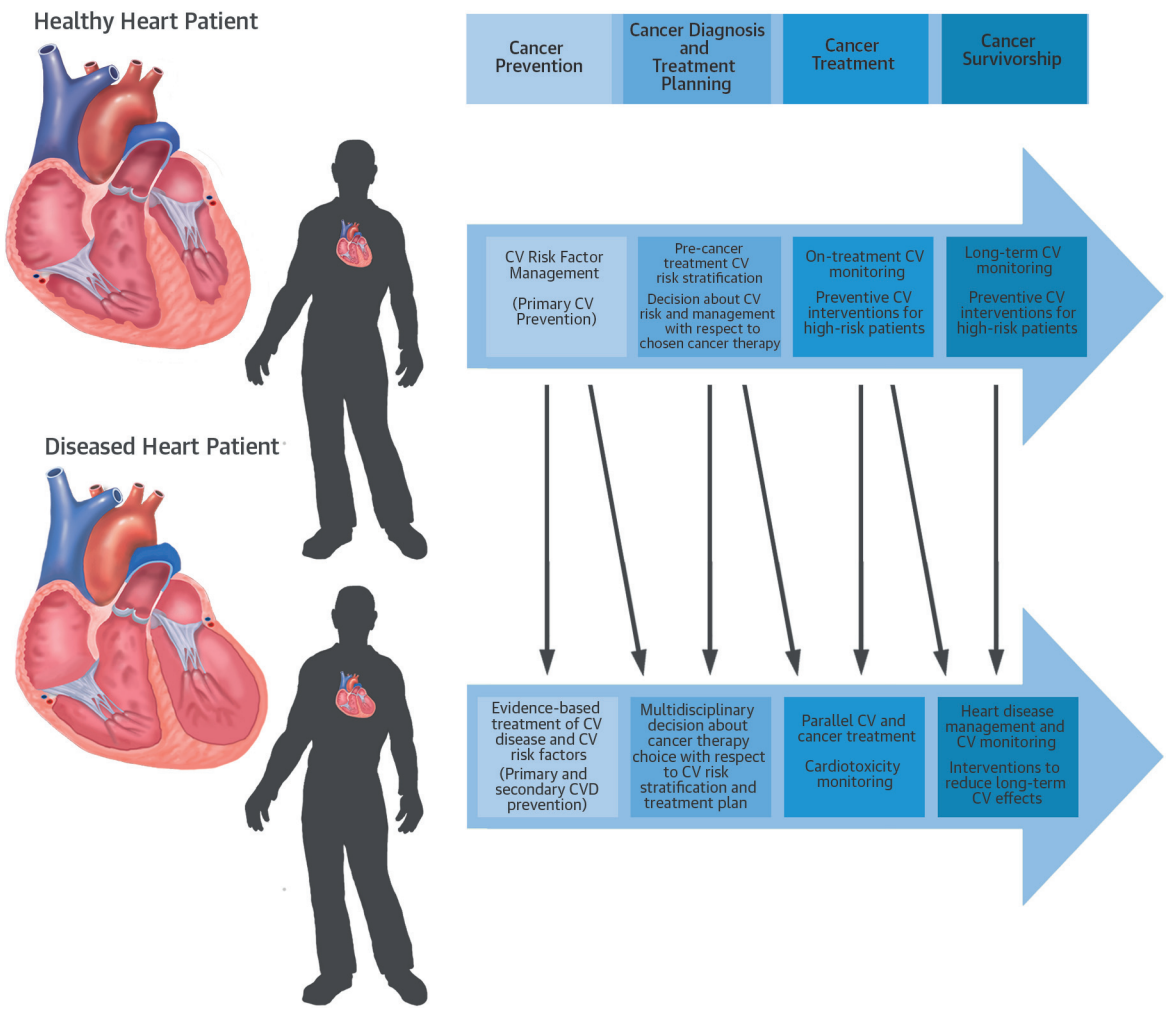
Since these early clinical and pathological observations, our knowledge about cardiotoxicity has seen impressive growth fueled by molecular investigations of traditional and numerous new cancer therapeutics (10–12), translational research using biomarkers and imaging for CV prediction and risk stratification (13–18), clinical trials evaluating the effects of cardioprotective strategies (19–22), as well as epidemiologic investigations into the burden of these diseases (23–26). In addition to cardiac dysfunction and heart failure, the spectrum of cardiovascular effects related to cancer therapies (spanning many cancer therapeutics and radiation treatments) includes, but is not limited to, arrhythmias, valvular heart disease, accelerated atherosclerosis, and pericardial disease. The reader is invited to in-depth reviews of these broad investigational areas (27–33).

The growth of research and clinical activities, evidenced by an exponential increase in the number of publications in the field (**Figure 2**), has set the foundation for a new discipline, aimed not only at screening, preventing, and treating CV effects of cancer therapies, but also at forming a partnership in providing comprehensive CV care for patients with cancer and cancer survivors (1–3).

EXISTING CARDIO-ONCOLOGY PROGRAMS: A VANGUARD?

Growing clinical demand has resulted in the emergence of dedicated cardio-oncology programs across the United States, frequently at tertiary/quaternary referral centers with both comprehensive cancer centers and dedicated heart failure programs. The MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, Vanderbilt-Ingram Cancer Center, University of Pennsylvania Abramson Cancer Center, and Dana-Farber Cancer Institute have pioneered these programs and have set critical groundwork in the field. However, these programs have formed in isolation, as currently there is no coordinating

FIGURE 1 Continuum of CV Care in Cardio-Oncology

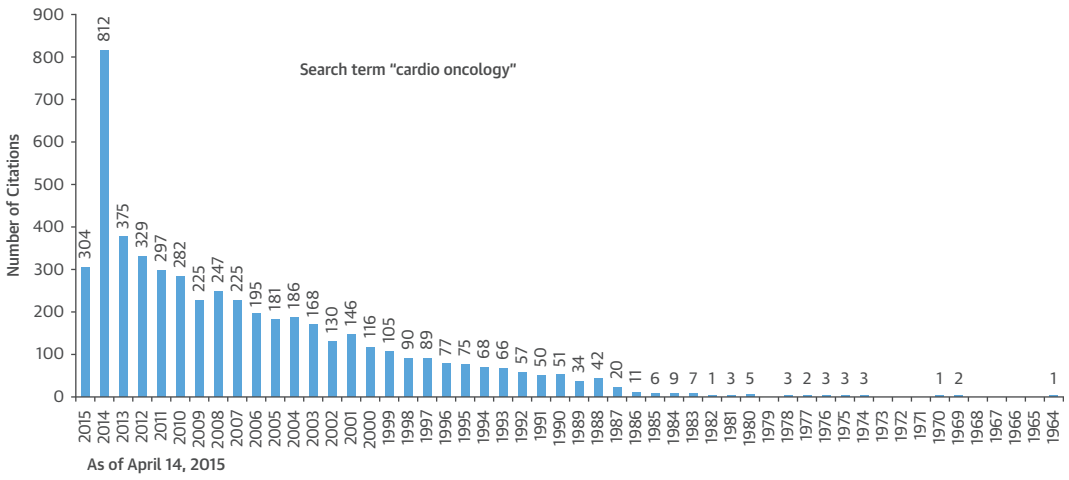


An example of the continuum of cardiovascular (CV) care on a timeline of cancer diagnosis, treatment, and survivorship. Patient A represents a patient with no existing cardiovascular disease (CVD), and Patient B represents a patient with a pre-existing CV condition. CAD = coronary artery disease; HF = heart failure.

professional association to guide and bridge their development. Despite this lack of external recognition, experience suggests that rapid growth in CV services occurs once a dedicated service is introduced. In 2000, the Department of Cardiology at MD Anderson Cancer Center had 4 general cardiologists managing 1,300 new consults, 3,700 inpatients, and 3,900 echocardiograms and electrocardiograms yearly (C. Iliescu, personal communication, December 2014). Since that time, this group has grown into a comprehensive CV service, including interventional, electrophysiology, and advanced heart failure services, with 2,500 new consults, 8,600 inpatient follow-up visits, and 75,000 imaging tests and CV procedures in 2014 (17,000 echocardiographic studies, 55,000 electrocardiograms, 2,000 cardiac catheterization and electrophysiology procedures, and 1,000 vascular and nuclear medicine studies) (C. Iliescu, personal communication, December 2014). Cardiomyopathy and cardiotoxicity represent 20% to 30% of the practice, with the remainder comprising pre-cancer therapy risk stratification and management, acute coronary syndromes, cardiac dysrhythmias, pericardial disease, and cardiac tumors.

Although these few, highly specialized CV centers are likely to provide excellent care for this patient cohort, the vast majority of patients with cancer and survivors are cared for in community-based practices,

FIGURE 2 PubMed Citations in "Cardio-Oncology"



Number of PubMed citations using search term "cardio oncology" by year.

rather than in academic settings. In such settings, the volume is expected to be much lower, affording physicians less experience in managing cardio-oncology concerns. Indeed, recent reports suggest that patients with cancer may be undertreated with regard to their CV risk compared with similar cancer-free cohorts (34,35). These observations have caused controversy and point to the need for better understanding and attention to the delivery of CV care for this heterogeneous patient population across diverse practice settings.

NATIONAL CARDIO-ONCOLOGY SURVEY

To evaluate the current state of cardio-oncology services, practices, and opinions within the wider ACC community, we conducted a nationwide online survey of 444 adult and pediatric cardiology division chiefs and CV fellowship program training directors. The rationale for focusing on division chiefs and training directors was because of their likely knowledge of existing clinical and educational cardio-oncology activities, as well as our working group's interest in their perception of the needs and potential barriers for development of cardio-oncology services, education, and training. Although the choice of this target population biased our sample in favor of academic institutions and limited representation of community awareness and efforts in our results, it provides an important insight into potential future opportunities for cardio-oncology knowledge dissemination from tertiary CV training centers into the community. The survey was conducted from May 5, 2014, to May 28, 2014, with reminders sent on May 13 and May 20. A total of 106 CV specialists completed the survey for an overall response rate of 24%. The majority of participants were cardiology fellowship training directors (44%) or cardiology division chiefs (25%) working at academic medical centers (76%). (All results are shown in the Online Appendix.) More than one-half described their heart failure program as involving transplant (56%) and their oncology program as representing a National Cancer Institute-designated Comprehensive Cancer Center (53%).

PERCEIVED IMPORTANCE OF CV CARE IN PATIENTS WITH CANCER. The majority of respondents (>70%) felt that CV implications of cancer treatment were a very important consideration in the continuum of treatment of patients with cancer, and two-thirds (65%) thought that access to consultants with specialized training would provide an advantage in caring for patients who experience CV complications from anticancer treatments. In the majority of centers, the estimated number of CV imaging tests for oncology patients was between 100 and 500 per year, with somewhat lower estimated numbers of CV consults.

CURRENT CARDIO-ONCOLOGY PROGRAMS AND TRAINING. In 35% of centers, cardio-oncology activities fall within pre-operative consultation services managed by general cardiology, whereas 27% of centers reported having an established, specialized cardio-oncology service with multiple clinicians. A total of 16% of respondents reported relying on a

single cardiologist with expertise in the area, and 12% currently offer no cardio-oncology services but plan to add them within the next year.

PERCEIVED LEVEL OF UNDERSTANDING AMONG FELLOW SPECIALISTS. A significant number of the participants (39%) did not feel confident in dealing with CV care specific to patients with cancer, and participants gave themselves an average rating when asked about their level of understanding of the effect of holding or stopping anticancer treatment on cancer outcomes. At the same time, cardiologists gave their peer oncologists an average rating about their understanding of the effect of slow or inadequate cardiology assessment on the development of CV complications in oncology patients. More than one-half (52%) of respondents agreed (vs. 9% who disagreed) that a cardio-oncology service or a dedicated clinician would improve the care of patients with cancer.

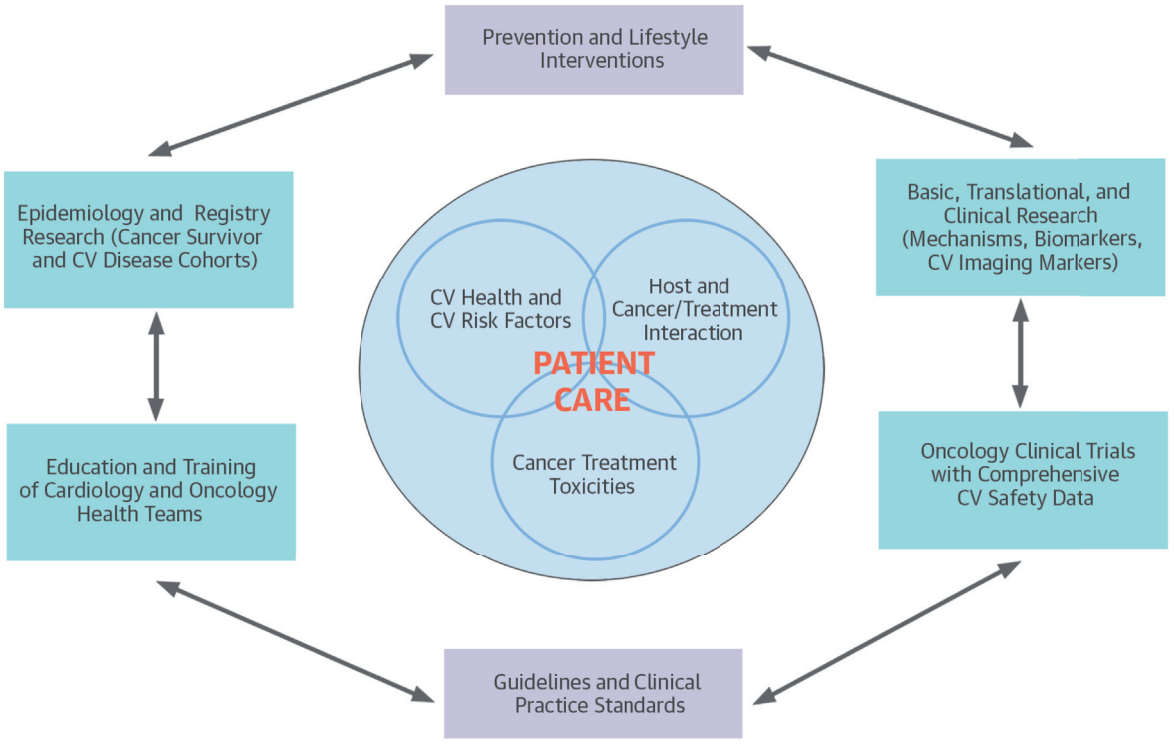
BARRIERS TO ESTABLISHMENT OR EXPANSION OF CARDIO-ONCOLOGY SERVICES. Lack of national guidelines and lack of funding were the most frequently cited barriers to the establishment of a cardio-oncology service (both cited by 44%), followed by

TABLE 1 Current and Future Opportunities in Advancing CV Care in Patients With Cancer and Cancer Survivors

Cardio-Oncology Area	Examples of Recent and Current Activities	Possible Future Steps
Best clinical care practices	• The ASCO Survivorship Guidelines Advisory Group is developing a clinical guidance document on prevention and monitoring of cardiac dysfunction in survivors of adult cancers. • The SCAI is developing a document on special considerations of cardio-oncology patients in the cardiac catheterization laboratory. • NCCN Guidelines for Survivorship, Version 1.2015, include a new algorithm with recommendations for the treatment of anthracycline-induced cardiac toxicity (37). • The ASE and the EACVI have published expert consensus documents on multimodality imaging in evaluation of cardiovascular complications of radiotherapy (38) and in patients during and after cancer therapies (39).	• Development of additional clinical practice documents in the areas of diagnosis, CV monitoring, prevention, and treatment of CV disease in patients with cancer and cancer survivors. This includes a number of focused, cancer treatment-related, and survivorship-related cardiotoxicity guidelines with multidisciplinary group inclusion. • Quality of care improvement initiatives with broader implementation of existing databases and development of new database models adapted for interdisciplinary care.
Research	• The NCI and NHLBI convened a workshop: "Cancer Treatment-Related Cardiotoxicity: Understanding the Current State of Knowledge and Developing Future Research Priorities" (31) to establish scientific priorities regarding cancer treatment-related cardiotoxicity. • NCI's Cardiotoxicity Working Group is currently funding several pilot studies of the utility of various imaging and biomarker techniques in cancer clinical trials (L. Minassian, personal communication, April 2015).	• Enhancement of efforts and funding in all areas including, but not limited to, outcomes and epidemiology, basic science, translational science, and clinical trials. • Critical integration and validation of data, mostly from single academic institutions, to confirm clinical effectiveness and inform clinical practice activities with eventual guideline generation.
Education	• MD Anderson and ICOS organize biannual conferences focused on CV effects of cancer therapies. • MD Anderson web-based audiovisual lecture series on MD Anderson Practices in Onco-Cardiology discuss topics relevant to heart disease in patients with cancer and cardiotoxicity (40). • ICOS holds monthly webinars with live discussions of clinical cases and cardio-oncology topics (41). • *Cancer and the Heart* textbook by MD Anderson authors addresses broad aspects of cardiotoxicity (42). • ACC.15 featured "Cardio-Oncology Intensive," a dedicated half-day session with multidisciplinary participation. • ASCO's CME modules focus on the oncologist's perspective and medical concerns related to CV toxicity (43,44).	• Further development of educational content for cardiology providers covering rapidly evolving areas, such as targeted therapeutics, novel cancer-treatment combination therapy regimens, prevention, and role of cardiologists in survivorship programs. • Further development of tools for knowledge dissemination, such as CME courses, online tools and applications, workshops, and integration with national and international conferences. • Collaboration with oncology professional societies in development and dissemination of educational materials for oncology providers.
Training	• Only a few institutions offer advanced training in cardio-oncology. There are no advanced training standards.	• Development of cardio-oncology-specific competencies, training assessment tools, and curricular milestones based on COCATS recommendations (36). This will include development of criteria and standardization of advanced training (Level II and III training). Successful examples of CV areas included in COCATS 4 include CV prevention, vascular medicine, critical care cardiology, and others (36).
Collaborations of stakeholders	• NCI-NHLBI Workshop on cardiotoxicity highlighted the role of partnership between different government and regulatory agencies and professional societies (31). • ASCO and ACC have formed a working group charged to explore opportunities for collaboration.	• Further collaborative efforts with cardiology and oncology professional societies in developing clinical practice standards and curricula for training programs. • Advocacy for policies supporting cardio-oncology care with government agencies and regulatory agencies. • Advancement of cardio-oncology research initiatives and funding by government and other sponsors.

ACC = American College of Cardiology; ASCO = American Society of Clinical Oncology; ASE = American Society of Echocardiography; CME = Continuing Medical Education; COCATS = Core Cardiovascular Training Statement; CV = cardiovascular; EACVI = European Association of Cardiovascular Imaging; ICOS = International CardiOncology Society; NCCN = National Comprehensive Cancer Network; NCI = National Cancer Institute; NHLBI = National Heart, Lung, and Blood Institute; SCAI = Society of Cardiac Angiography and Interventions.

CENTRAL ILLUSTRATION **Overview of the Spectrum of Cardio-Oncology: Bench to Bedside to Community**



Barac, A. et al. J Am Coll Cardiol. 2015; 65(25):2739–46.

Partnerships across and within the disciplines of cardiology and oncology in the areas of research (basic, translational, clinical, and population science), education and clinical training, and guidelines and clinical documents development as a potential solution to unmet needs and advancement in patient care. CV = cardiovascular.

limited interest (38%), infrastructure (36%), and educational opportunities (29%). Only 7% felt there were no barriers. Many programs reported having no formal training in cardio-oncology (43%), with some institutions offering exposure during regular clinical rotations (43%) and a small number including lectures in cardio-oncology as part of the core curriculum (11%). Importantly, 70% of respondents reported that they would be likely to use educational material for their fellows and staff, if those were available.

More than one-quarter (27%) of respondents (n = 29) offered additional comments to express needed support in the field of cardio-oncology, specifically the need for educational materials and dedicated meetings (25%), training and curriculum (22%), clinical relevance and growth (19%), and the development of guidelines (13%). Two respondents (6%) listed concerns about excessive splitting of the CV specialty into subspecialties.

ROADMAP TO THE NEXT LEVEL

The survey results document a widespread appreciation of the importance of CV concerns in patients with cancer and a recognized need to improve the care of these patients through provision of specialized services. However, the survey also notes significant barriers. Plans to develop cardio-oncology must recognize both the opportunities and the potential hurdles. The ACC's recognition of the importance of this area and dedication to its advancement is manifest by the recent creation of a member section in cardio-oncology, which is a major step forward.

In planning for this section, the Cardio-Oncology Working Group considered current and future opportunities in broad areas of best clinical practices, research, education, and training (Table 1). The activities listed represent an arbitrary and narrow sample that is evolving rapidly (and will be outdated soon)

but aim to give an insight into successful seminal efforts that now need to be broadened (**Central Illustration**). For example, our survey identified a need for training in cardio-oncology that currently exists only at a few comprehensive cancer centers that possess a critical concentration of expert faculty, clinical volume, and complexity. Expansion of these efforts is necessary to meet the growing demand for trained CV specialists. The establishment of the key competencies within cardio-oncology and the tools necessary to assess training and establish progress, following the Core Cardiovascular Training Statement recommendations (36), will be required to allow further successful growth of the field. Similarly, within broad areas of research and clinical standards in cardio-oncology, there is a need for critical validation and integration of the data from single academic institutions, further development of methods and standards, and strategic implementation and dissemination of knowledge.

The Cardio-Oncology member section will serve as a professional home for the growing number of specialists and allow them to share best practices, develop educational tools and practice standards, design training programs, advocate for cardio-oncology, as well as collaborate with oncology specialists. It is through these advancements and critical partnerships within cardiology and across specialties that a value-based proposition of improved patient care and outcomes will be fulfilled.

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KEY WORDS cancer survivorship, cardio-oncology, cardiovascular risk prevention, cardiovascular toxicity

APPENDIX For the Cardio-Oncology Survey Report, please see the online version of this article.