JACC: CARDIOONCOLOGY
PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION.

VOL. 4, NO. 3, 2022

VIEWPOINT

The Impact of the Cancer Moonshot on Cardio-Oncology Science

Lori M. Minasian, MD,[a] Bishow B. Adhikari, PhD,[b] Eileen P. Dimond, BSN, MSN,[a] Nonniekaye Shelburne, CRNP, MS, AOCN,[c] Scarlet Shi, PhD,[b] Patrice Desvigne-Nickens, MD[b]

CANCER MOONSHOT

In 2016, Vice President Joseph Biden launched the Cancer Moonshot with the goal of accelerating the rate of progress against cancer.[1] It was intended to catalyze areas of cancer research that could rapidly scale up and have a significant impact on the treatment and care of cancer patients. The US National Cancer Institute (NCI) developed a series of expert panels to identify key areas of focus and gather stakeholder feedback through meetings, town halls, and a public website.[2] The priority research areas are:

- Establish a network for direct patient engagement;
- Create an adult immunotherapy network;
- Create a pediatric immunotherapy discovery and development network;
- Develop ways to overcome cancer's resistance to therapy;
- Build a national cancer data ecosystem;
- Intensify research on the major drivers of childhood cancers;
- Minimize cancer treatment's debilitating side effects;
- Enhance prevention and early detection of hereditary cancers;
- Expand use of proven cancer prevention and early detection strategies;
- Support retrospective analyses of patient data and biospecimens from past clinical trials to predict future patient outcomes;
- Generate human tumor atlases; and
- Develop new enabling cancer technologies.

The Cancer Moonshot implementation plan had 3 primary goals: accelerate scientific discovery, foster greater collaboration, and improve data sharing. To date, over 70 consortia and 240 new projects have been funded through this initiative,[3] including cross-grantee and data-sharing collaborations. The priority areas emphasize the need to accelerate the development of novel therapeutics for which unique and currently unknown cardiovascular complications may occur. The priority to "minimize cancer treatment-related side effects" has resulted in one consortium that is developing approaches to analyze patient-reported symptomatic adverse events along with clinician-reported adverse events, whereas a second consortium is implementing symptom management approaches in the delivery of routine cancer care.

Although the Cancer Moonshot did not explicitly call out cardio-oncology as a focus, the cardiovascular complications from cancer treatment impact the quality of life and the survival of cancer patients, and directly pertain to the priority area of minimizing cancer treatment's debilitating side effects. Before the initiation of the Cancer Moonshot, many of the cardiovascular complications of specific chemotherapies and radiation were well known, but effective strategies for mitigating these complications were lacking.[4,5] To address these challenges, staff from the National Heart, Lung, and Blood Institute and the NCI convened a workshop in 2013 to identify knowledge gaps and prioritize the research opportunities by bringing together clinicians and investigators in cardiovascular disease and cancer.[6] Over 40 scientific research gaps were identified. The workshop

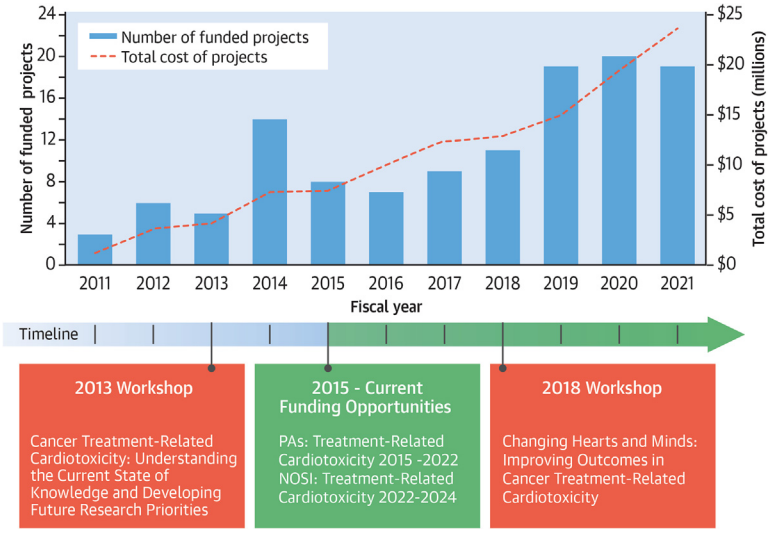
From the [a]Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland, USA; [b]Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, Maryland, USA; and the [c]Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, Maryland, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2022.08.004

JACC: CARDIOONCOLOGY, VOL. 4, NO. 3, 2022
SEPTEMBER 2022:413–416

FIGURE 1 NIH Funding for Cancer Treatment-Related Cardiotoxicity Research Projects (FY 2011-2021)



The number of funded research projects are shown in **blue bars**. The total funding for each year is shown as the **red line** and adjusted for the Biomedical Research and Development Price Index. Complementary to the chart is a timeline for workshops and availability of targeted funding opportunities. Awards for a subsequent budget period within a previously approved project are not counted as new awards. This figure is adapted with permission from Adhikari et al.[7] NIH = National Institutes of Health; NOSI = Notice of Special Interest; PA = Program Announcement.

facilitated the development of collaborations between cardiovascular and cancer researchers and identified translational projects as a critical need.[6] When the initial funding opportunity announcements for Improving Outcomes in Cancer Treatment-Related Cardiotoxicity (PA-16-035, PA-16-036) were released, investigators were strongly encouraged to collaborate through the multiple principal investigator mechanisms, including at least 1 cardiovascular investigator and 1 cancer investigator. These funding opportunities were renewed, and together with the first workshop and a follow up workshop in 2018, resulted in an increased number of funded projects in the basic and translational science of cardiovascular complications from cancer treatment (**Figure 1**).[7] These basic and translational projects focus on the early and late mechanisms of cardiovascular injury, the influence of sex differences, and innate immune mechanisms,[7] which are critical to identify effective means to detect and mitigate cardiovascular disease. Consistent with the increased number of funded research projects, the total amount of research funding (in 2021 dollars) in cardio-oncology science has been increasing over the last 10 years (**Figure 1**).

One notable finding in this portfolio of projects is that many continue to focus on anthracycline cardiotoxicity. Anthracyclines have been an essential component of treatment for breast cancer, leukemia, lymphoma, sarcoma, and other malignancies. As clinicians have a better understanding of the long-term risks from anthracyclines, and newer therapies are available for specific cancer subtypes, oncologists are reassessing anthracycline use in different clinical scenarios. Despite overall declines in cancer-related cardiovascular mortality, chemotherapy-induced cardiotoxicity remains an important target to further improve survivorship outcomes.[8]

Even with the efforts to stimulate rigorous research projects in cardio-oncology science, the pace of cancer drug development can result in rapid approval and use of regimens without a full understanding of the potential cardiovascular risks. Although the acute adverse events are carefully collected and reported on cancer clinical trials, assessment of the extent of chronic or progressive adverse effects and long-term complications remains challenging,[9] but needed. Moreover, many cancer patients receive combination therapy and multiple regimens over time. Each agent carries different cardiovascular risks; both the combination and the sequential receipt of these agents may have a cumulative impact and potentially impact overall survival. Altered immunity, severe hormonal

deprivation, and frailty are examples of conditions that influence cardiovascular resilience and are underinvestigated.

Typically, patients on cancer clinical trials have fewer comorbidities; hence, the risk-benefit of novel regimens may not be fully understood in patients who do have comorbidities. A national survey of over 5,000 cancer patients demonstrated that most (65%) have 1 or more comorbidities, the most common being hypertension.[10] Pre-existing cardiovascular risk factors and disease increase the susceptibility of injury from cardiotoxic cancer therapies. As a result, the dose and schedule of cancer treatment may need to be modified when delivering newer regimens to broader populations.

With the rapidly changing landscape of novel approaches to cancer treatment, the need for rigorous and clinically meaningful cardio-oncology science is greater than ever. Yet, it can be quite daunting to understand how best to address the spectrum of issues in cardio-oncology.[11] Although overall cancer death rates are decreasing,[12] cardiovascular mortality appears to be overtaking cancer mortality,[13] particularly in older patients. There is a significant, ongoing need to understand and manage cardiovascular complications from novel cancer therapies in patients during and after treatment.

A key principle from the Cancer Moonshot is collaboration. One way to approach the development of collaborative cardio-oncology research is through understanding risk. The cardiology community has long used models of risk to predict mortality from cardiovascular disease. The oncology community has long triaged cancer treatment based upon disease stage and risk of recurrence. Together, cardiology and oncology experts can develop new models for guiding both cardiovascular protection and cancer treatment with data generated from the next generation of cardio-oncology studies.

Many of the investigators within the NCI Clinical Trials Network and the NCI Community Oncology Research Program (NCORP) are invested in partnering with cardiology and cardio-oncology to determine how best to evaluate cardiovascular toxicity within cancer treatment trials, and symptom management and toxicity mitigation trials. Researchers are embedding cardiotoxicity endpoints and risk assessments into treatment trials and seeking supplemental funding for specific cardiovascular assessment. Cardiovascular toxicity is a priority research area within the NCORP symptom science portfolio. NCORP incorporates community practices to ensure that research goes beyond academic medical centers, including minority underserved NCORP sites that recruit from underrepresented populations, who often have a high prevalence of cardiovascular risk factors.

The cancer patient's risk of cardiovascular adverse events from treatment must be balanced with the necessity to treat the patient's cancer (including the aggressive nature of that cancer and the risk for cancer recurrence). Frequently, the level of acceptable potential toxicity can be high if the patient has a cancer that is highly aggressive or refractory to treatment. For example, 1 of the several tyrosine kinase inhibitors used in chronic myelogenous leukemia, ponatinib, has significant cardiovascular risk, and yet, remains a useful agent for those patients with refractory disease.[14]

Now is the time for cardiovascular and cancer investigators to jointly develop studies grounded in basic and translational science that evaluate cardiovascular injury and resilience from new anticancer agents and combination therapy. Potential cardioprotective mechanisms need to be evaluated prospectively both during cancer treatment and after completion. There remains a great need to incorporate both relevant cardiovascular and cancer endpoints while evaluating new therapies and conducting cardio-oncology studies.[15] Research gaps identified in the subsequent 2018 NCI-National Heart, Lung, and Blood Institute workshop (**Figure 1**) highlight this ongoing need,[16] including: developing cardiovascular risk assessment and stratification tools; developing and implementing strategies for the prevention and management of cardiovascular risk factors; and developing and validating screening and detection modalities for monitoring cardiovascular injury during and after cancer treatment, both short and long term.

With the growth of cardio-oncology clinics in academic and community settings, there are more opportunities for collaboration, including facilitating strategies to assess cancer patients' baseline cardiovascular function and supporting the ongoing use of cardioprotective interventions during and after cancer treatment. Longitudinal studies can be developed to better understand the natural history of subacute cardiovascular injury and the resilience of cardiovascular function based upon both individual patient factors and cancer therapies, and these studies need to include representative populations. As learned from the COVID-19 pandemic, structural bias in access to health services and literacy remains a challenge that needs urgent attention as it contributes to underrepresented groups having poorer outcomes.

The cardio-oncology community has grown over the past decade, initiating important studies and clinical trials, and developing guidelines for assessing the cardiovascular status and monitoring of patients receiving cardiotoxic cancer treatment. *JACC: CardioOncology* has been at the forefront providing a variety of clinical and scientific resources.[17] As the NCI prepares for the reignited Cancer Moonshot,[18] the goals are identified as: 1) reduce the death rate from cancer by at least 50% in the next 25 years; and 2) improve the experience of people and their families living with and surviving cancer. Collaboration across cardio-oncology science has the potential to develop new risk models incorporating both cardiovascular and cancer risk to facilitate better delivery of anticancer therapy while minimizing cardiovascular complications, and thus plays a pivotal role in improving the experience of cancer patients and survivors by reducing cancer treatment-related cardiovascular morbidity and mortality.

ACKNOWLEDGMENTS The authors would like to thank Gwen Moulton for editorial assistance in preparing the manuscript and Jack Lee for assistance in developing the figure.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Although the Cancer Moonshot is an NCI initiative, the views expressed in this paper are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Cancer Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Lori Minasian, Division of Cancer Prevention, National Cancer Institute, 9609 Medical Center Drive, 5E-342, MSC-9784, Bethesda, Maryland 20892-9784, USA. E-mail: minasilo@mail.nih.gov. Twitter: @NCI-SymptomMgmt, @theNCI, @NIH_NHLBI.

REFERENCES

1. National Cancer Institute. Cancer Moonshot℠. Accessed June 9, 2022. https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative

2. Lowy DR, Singer DS. Implementing the Cancer Moonshot and beyond. *Lancet Oncol*. 2017;18:e622-e623.

3. Sharpless NE, Singer DS. Progress and potential: the Cancer Moonshot. *Cancer Cell*. 2021;39:889-894.

4. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. *Nat Rev Cardiol*. 2015;12:547-558.

5. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol*. 2009;53:2231-2247.

6. Shelburne N, Adhikari B, Brell J, et al. Cancer treatment-related cardiotoxicity: current state of knowledge and future research priorities. *J Natl Cancer Inst*. 2014;10;106(9):dju232.

7. Adhikari B, Shi S, Dimond EP, Shelburne N, Desvigne-Nickens P, Minasian LM. Spectrum of NIH-funded research in cardio-oncology: a basic, clinical, and observational science perspective. *Heart Fail Clin*. 2022;18(3):515-528. https://doi.org/10.1016/j.hfc.2022.01.001

8. Vo JB, Ramin C, Barac A, Berrington de Gonzalez A, Veiga L. Trends in heart disease mortality among breast cancer survivors in the U. S., 1975-2017. *Breast Cancer Res Treat*. 2022;192:611-622.

9. Thanarajasingam G, Minasian LM, Baron F, et al. Beyond maximum grade: modernising the assessment and reporting of adverse events in haematological malignancies. *Lancet Haematol*. 2018;5:e563-e598.

10. Unger JM, Hershman DL, Fleury ME, Vaidya R. Association of patient comorbid conditions with cancer clinical trial participation. *JAMA Oncol*. 2019;5(3):326-333.

11. Abe JI, Yusuf SW, Deswal A, Herrmann J. Cardio-oncology: learning from the old, applying to the new. *Front Cardiovasc Med*. 2020;7:601893.

12. American Cancer Society, Centers for Disease Control and Prevention, North American Association of Central Cancer Registries, and National Cancer Institute. Annual report to the nation on the status of cancer. Accessed June 9, 2022. https://seer.cancer.gov/report_to_nation/

13. Strongman H, Gadd S, Matthews AA, et al. Does cardiovascular mortality overtake cancer mortality during cancer survivorship?: an English retrospective cohort study. *J Am Coll Cardiol CardioOnc*. 2022;4:113-123.

14. Banegas MP, Rivera DR, O'Keeffe-Rosetti MC, et al. Long-term patterns of oral anticancer agent adoption, duration, and switching in patients with CML. *J Natl Compr Canc Netw*. 2019;17:1166-1172.

15. Minasian L, Dimond E, Davis M, et al. The evolving design of NIH-funded cardio-oncology studies to address cancer treatment-related cardiovascular toxicity. *J Am Coll Cardiol CardioOnc*. 2019;1:105-113.

16. Shelburne N, Simonds NI, Adhikari B, et al. Changing hearts and minds: improving outcomes in cancer treatment-related cardiotoxicity. *Curr Oncol Rep*. 2019;21:9.

17. Ky B. JACC: CardioOncology: reflections on tremendous growth with gratitude. *J Am Coll Cardiol CardioOnc*. 2022;4:146-148.

18. The White House. Fact sheet: President Biden reignites cancer moonshot to end cancer as we know it. February 2, 2022. Accessed June 9, 2022. https://www.whitehouse.gov/briefing-room/statements-releases/2022/02/02/fact-sheet-president-biden-reignites-cancer-moonshot-to-end-cancer-as-we-know-it/

KEY WORDS Cancer Moonshot, cardio-oncology, cardiotoxicity, NCI-NHLBI workshop