

Voice of the Patient Report *Released June 2023*

**Reducing Cardiac Late Effects
in Pediatric Cancer Survivors**



Read about Ruth and Charlene on page 25.

Externally-led Patient-Focused Drug Development Meeting
September 15, 2022



**"People have no idea of the
late effect ticking time bomb
[inside my daughter]."**

- Lynn, Parent

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Partnering Organizations: American Academy of Pediatrics, American Society of Clinical Oncology, American Society of Pediatric Hematology/Oncology, The Andrew McDonough B+ Foundation, and Teen Cancer America

This document represents the summary report written by Children's Cancer Cause stemming from an Externally-led Patient-Focused Drug Development (EL-PFDD) meeting on reducing cardiac late effects among pediatric cancer survivors held virtually on September 15, 2022. This report reflects the host organization's account of the perspectives of survivors and caregivers who participated in the public meeting and provided input in the 30-day period following the meeting.

A plain text version of this document was submitted in March 2023 as patient experience data for consideration pursuant to section 569C of the Federal Food, Drug and Cosmetic Act to:

- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)
- U.S. Food and Drug Administration (FDA)



Children's Cancer Cause is a leading national advocacy organization working to achieve access to less toxic and more effective pediatric cancer therapies; to expand resources for research and specialized care; and to address the unique needs and challenges of childhood cancer survivors and their families.

Our vision is a long, healthy life for every child with cancer. Learn more:

 [**childrenscancercause.org**](https://www.childrenscancercause.org)

This is the second EL-PFDD we have hosted, following a successful meeting in 2018 focused on chemotherapy-induced hearing loss in childhood cancer. Both meetings and reports are available at:

 [**childhoodcancerpfdd.org**](https://www.childhoodcancerpfdd.org)

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Review of this report was provided by partnering organizations: **American Academy of Pediatrics**, **American Society of Clinical Oncology**, **American Society of Pediatric Hematology/Oncology**, **The Andrew McDonough B+ Foundation**, and **Teen Cancer America**. Children's Cancer Cause board members **Susan L. Weiner**, PhD, and **Dan Wechsler**, MD, PhD, also provided review.

James Valentine, JD, MHS and Larry Bauer, RN, MS are employed by **Hyman, Phelps & McNamara, P.C.**, a law firm that represents sponsors who are developing drugs as well as patient advocacy organizations, including Children's Cancer Cause. Wendy K.D. Selig, MSJ, receives consulting revenues from a variety of oncology patient advocacy organizations (including Children's Cancer Cause) and for-profit companies through her firm, **WSCollaborative**.

Disclosures: Authors and collaborators have nothing to disclose.



A Message of Thanks

On September 15, 2022, individuals who have experienced cardiac late effects after pediatric cancer treatment – both survivors and caregivers – met virtually to discuss their experience living with these conditions and their perspectives on current and future treatments. The Externally-led Patient-Focused Drug Development (EL-PFDD) meeting hosted by Children’s Cancer Cause provided an opportunity for people affected by the challenging impact of cardiac late effects to come together, share their stories, and describe their experiences, helping to shape the future work of regulators, clinicians, industry colleagues, and the advocacy community.

Many of the drugs currently being used to treat pediatric cancers were developed 40 to 50 years ago. While these treatments are often successful in extending survival for childhood cancer patients, this longer life often comes with the steep downstream personal costs of complex and serious side effects much later in life. Moving forward, we know that we urgently need less toxic and more effective solutions to treat childhood cancers; likewise, we also desperately need better treatments for people living with cardiomyopathy and other cardiac late effects from their cancer therapies.



"We hope this effort will inspire all relevant stakeholders to enhance efforts to reduce or prevent, identify early, manage, and treat cardiac late effects."

- Steve Wosahla, CEO, Children's Cancer Cause

We are so grateful to the many courageous survivors and caregivers who came forward to describe how these late effects impact their quality of life and provide their insights about how we can collectively do better to reduce cardiac late effects by **improving our understanding, management, and treatment** of these serious long-term sequelae of cancer treatment.

We thank the many U.S. Food and Drug Administration (FDA) leaders and staff who worked with us for months as we planned the EL-PFDD meeting. We especially appreciate Greg Reaman, MD, FASCO, for providing opening remarks, and Shannon Sparklin of the Patient-Focused Drug Development Program Staff at FDA, for her guidance leading up to the meeting.

A Message of Thanks, continued

We are grateful for our collaborating partner organizations, the **American Academy of Pediatrics**, **American Society of Clinical Oncology**, **American Society of Pediatric Hematology/Oncology**, **The Andrew McDonough B+ Foundation**, and **Teen Cancer America**, who provided expertise on meeting content and provided extensive outreach to help engage and mobilize their members and constituents in better understanding the patient perspective around cardiac late effects.



We greatly appreciate the expert comments of **Dr. Smita Bhatia**, Director, Institute for Cancer Outcomes and Survivorship, at the School of Medicine, University of Alabama at Birmingham, and **Dr. Saro Armenian**, Chair, Department of Pediatrics and Director, and Division of Outcomes Research, City of Hope Comprehensive Cancer Center, who shared their clinical expertise on cardiac late effects and its treatment for the meeting. James Valentine and Larry J. Bauer of Hyman Phelps & McNamara were instrumental in the planning and execution of this meeting, with James joining me as co-moderator and Larry providing expert strategic support and summary comments.

Logistics for the virtual meeting were seamlessly coordinated by **John Dudley** and his team at Dudley Digital Works. Julie Taylor of Children's Cancer Cause oversaw and executed this project with the tremendous commitment and professionalism our staff is known for, guiding its development from initial concept through implementation. Support for the meeting and writing of this report was provided by Wendy K.D. Selig of WS Collaborative. The communications for this meeting and the design of this report was produced by Children's Cancer Cause's Jessica Kean.

Our thanks go to our sponsors for helping to make this meeting possible. This event received financial support from **Day One Biopharmaceuticals**, **CHC: Creating Healthier Communities**, the **Stewart Initiative for Childhood Cancer Survivors** (a program of Children's Cancer Cause), and **Whole Foods Market**.

A Message of Thanks, continued

Pediatric cancer patients and their caregivers, confronted with serious and debilitating cardiac late effects from their cancer treatments, often feel **alone**, **confused**, and **anxious** about how damage from radiation and chemotherapy will impact their long-term health. There continues to be a tremendous **unmet medical need** for people living with the late effects of childhood cancer treatment in general, and cardiac late effects specifically. As one of our panelists shared ahead of the meeting, "the treatments that saved my life seem to be slowly stealing it."

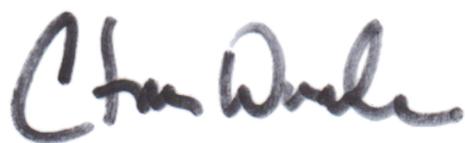
Children's Cancer Cause remains committed to partnering with patients, survivors, and caregivers to ensure that their perspectives and experiences are meaningfully included in addressing diseases and treatments that impact their lives.

Coming together in a public forum to describe the impact of cardiac late effects among survivors of childhood cancer helps to strengthen the shared sense of community and purpose to improve options with new, less toxic treatments, and other strategies and interventions to address late effects and improve health outcomes.

We hope this effort will inspire all relevant stakeholders to enhance efforts to reduce or prevent, identify early, manage, and treat cardiac late effects.

We hope and expect that this Voice of the Patient report will impact the way stakeholders think about this population's needs, encourage future research, and advance successful new product development for people living with these late effects.

Sincerely,



Steve Wosahla
Chief Executive Officer
Children's Cancer Cause



Executive Summary

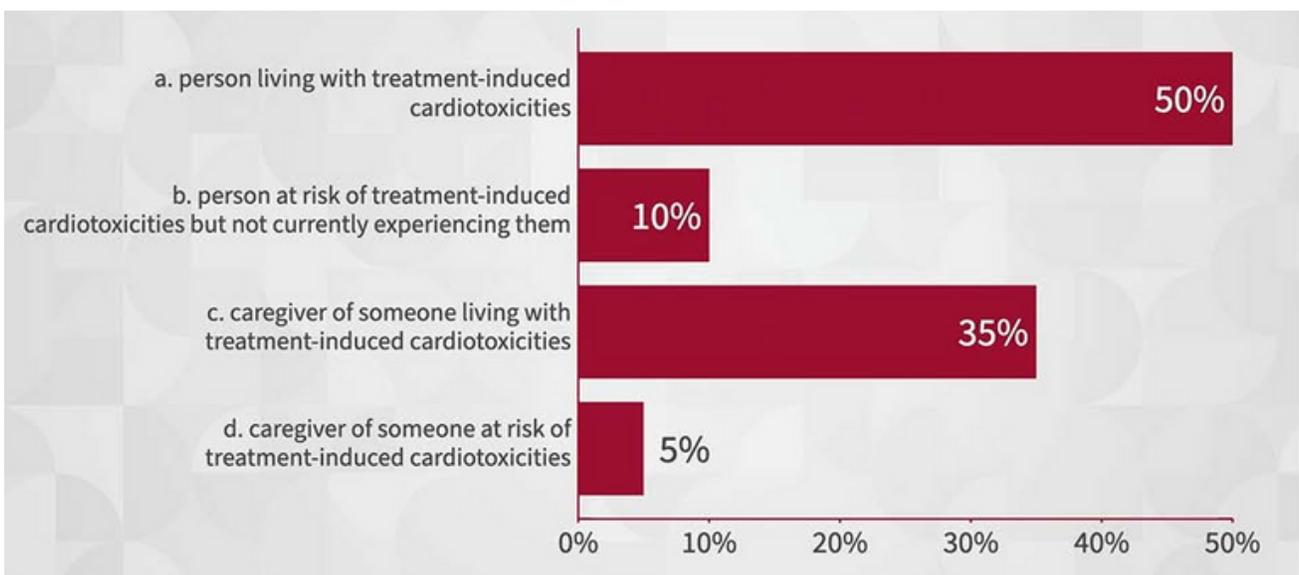
During this meeting, survivors and caregivers discussed the symptoms, impacts on daily life, management approaches, and priorities for treatment of cardiac late effects among pediatric cancer survivors.

Executive Summary

Medical progress has resulted in increased survival and the chance of long life for many pediatric cancer survivors. While aggressive treatments are often successful in achieving remission, **survival may come at the expense of serious side effects throughout their lives.** Today, an estimated 500,000 survivors of pediatric cancer (defined within this report as *any patient who has experienced pediatric cancer*) are facing a lifetime of health challenges, including serious cardiac late effects from cancer therapy.

To bring to light the experiences and concerns of pediatric cancer survivors living with cardiac late effects and their caregivers, Children’s Cancer Cause hosted a virtual Externally-led Patient-Focused Drug Development (EL-PFDD) meeting on September 15, 2022. During this meeting, survivors and caregivers discussed the **symptoms, impacts on daily life, management approaches, and priorities** for treatment of cardiac late effects among pediatric cancer survivors. There were approximately 150 attendees at this virtual meeting including pediatric cancer survivors/caregivers, staff from the FDA, industry representatives, health care providers, and scientists.

Among the survivor/caregiver cohort of participants, half identified as a person currently living with treatment-induced cardiotoxicities:



Executive Summary: Presentations

The meeting included an opening presentation from **Gregory Reaman, MD**, then of FDA's Oncology Center of Excellence (OCE) within the Center for Drug Evaluation and Research (CDER), in which he discussed the serious challenges childhood cancer survivors face in terms of late effects that impact the length and quality of their lives after cancer treatment. He emphasized the importance of evaluating the long-term safety of new pediatric cancer treatments, in addition to their efficacy. He shared that this PFDD meeting is valuable to the FDA, like other PFDDs, to learn from people living with cardiac late effects and their care partners, helping the FDA to appropriately **evaluate meaningful clinical benefit when reviewing new products**.

Two clinical presentations offered PFDD participants an **overview of the causes and risks** associated with cardiac late effects for pediatric cancer patients, as well as opportunities for improving outcomes for these individuals.

Dr. Smita Bhatia (University of Alabama at Birmingham, pictured at right) described how people are **at risk for cardiac late effects** after chemotherapy treatment, especially when that treatment includes anthracyclines. Additional risks of cardiac late effects are associated with radiation therapy to the chest, patients being at a young age when they received cancer treatment, those who are female, and those who may have other cardiovascular risk factors. Pediatric patients who undergo cancer treatment may develop cardiac necrosis and fibrosis in the heart, with scarring leading to a dilated heart and eventual cardiomyopathy. Research to better understand and predict risk is continuing in hopes of improving the ability to screen patients at risk for cardiac late effects and intervene sooner to mitigate those effects. Research on prevention is especially needed among non-white populations.

Dr. Saro Armenian (City of Hope Comprehensive Cancer Center) discussed various interventions to mitigate the risk of cardiac late effects, including use of emerging **technology-enabled cardiac monitoring**. He also emphasized the importance of early and ongoing cardiac screening, as well as engaging a multi-disciplinary approach for long-term surveillance of childhood cancer survivors.



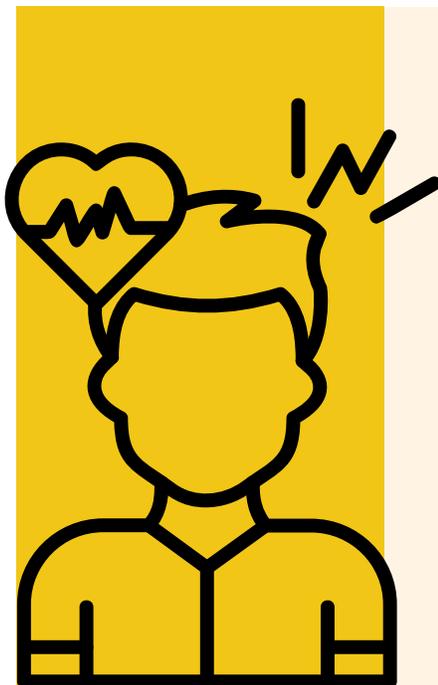
Executive Summary: Format

The bulk of the meeting involved moderated panel and group discussions among people living with cardiac late effects and their caregivers. The first of two sessions focused on the health effects and daily impacts of cardiac late effects. The second focused on patient and caregiver perspectives on current and future treatments/interventions. A total of 10 panelists (six patients and four caregivers) prepared and presented pre-recorded five-minute testimonials about their experiences. An additional 10 individuals served as live Zoom panelists to lead off the group discussion segments.



First Session: Living with Cardiac Late Effects

Participants identified many problems related to living with cardiac late effects, including dealing with key symptoms of **rapid heart rate, shortness of breath, fatigue, brain fog, chest pain, depression, and anxiety**. **Fear of the unknown** was a common theme as multiple participants described concern about progression of cardiac disease.



Second Session: Current & Future Approaches to Prevention & Treatment

Speakers described tremendous **unmet needs** among survivors with cardiac late effects. They noted insufficient current treatment options that fail to fully address symptoms or stop progression of cardiovascular disease. Current mitigating treatment options such as **valve replacement, heart transplant** and other cardiac surgeries are highly invasive and risky and are often complicated by co-morbidities and other medical issues. **Participants emphasized the importance of continuing research and innovation in this area.**

Executive Summary: Key Messages

Cardiac late effects may affect every part of a pediatric cancer survivor's life and pose many challenges that may impact the survivor and the entire family for a lifetime.



Individuals living with these late effects face a wide range of significant **physical, emotional, quality of life, and logistical burdens** due to cardiac late effects which may prevent them from living a full and independent life. Too often, managing their ongoing health is central to their daily lives. This is a devastating quality of life consequence for survivors, who are forced to make difficult sets of decisions and trade-offs.

While the effects of childhood cancer last a lifetime, survival may come at great cost. Survivors and caregivers are grateful for surviving cancer, yet they also feel that they **lack information** to prepare for the future and often feel betrayed by their experience. They often feel that there are no good choices and express **disappointment and frustration** that the same treatments used to beat the cancer also cause serious persistent new health problems that worsen over their lifetime. Treatment provides them the benefit of longer life, but this is accompanied by the **trauma** caused by suffering from serious life-threatening health conditions resulting from that treatment. For many parents, this trauma is compounded by feelings of **guilt and anxiety**, as they lament the difficulty of making the decision to allow critically important cancer treatments to be given, at the same time worrying about how late effects of treatment will affect their children's futures.

Pediatric cancer survivors rely on a wide range of medical interventions to manage and mitigate their cardiac late effects: routine heart medications for controlling blood pressure, managing cholesterol and diabetes, and reducing fluid build-up in the body. More significant interventions can include **advanced heart failure treatments, continuous IV infusions, pacemaker placement, valve replacement, and cardiac transplant**. Survivors are concerned about how well current medications and other interventions control their cardiac issues as well as the side effects from these medications.



Executive Summary: Key Messages

For survivors and caregivers, the most important potential new treatments are **protective treatments** to prevent heart effects from cancer treatments as well as less toxic cancer treatments with reduced impact on heart health. Improved treatment for symptoms of cardiac late effects and the need to stop further progression of heart disease are also important from the survivor perspective.

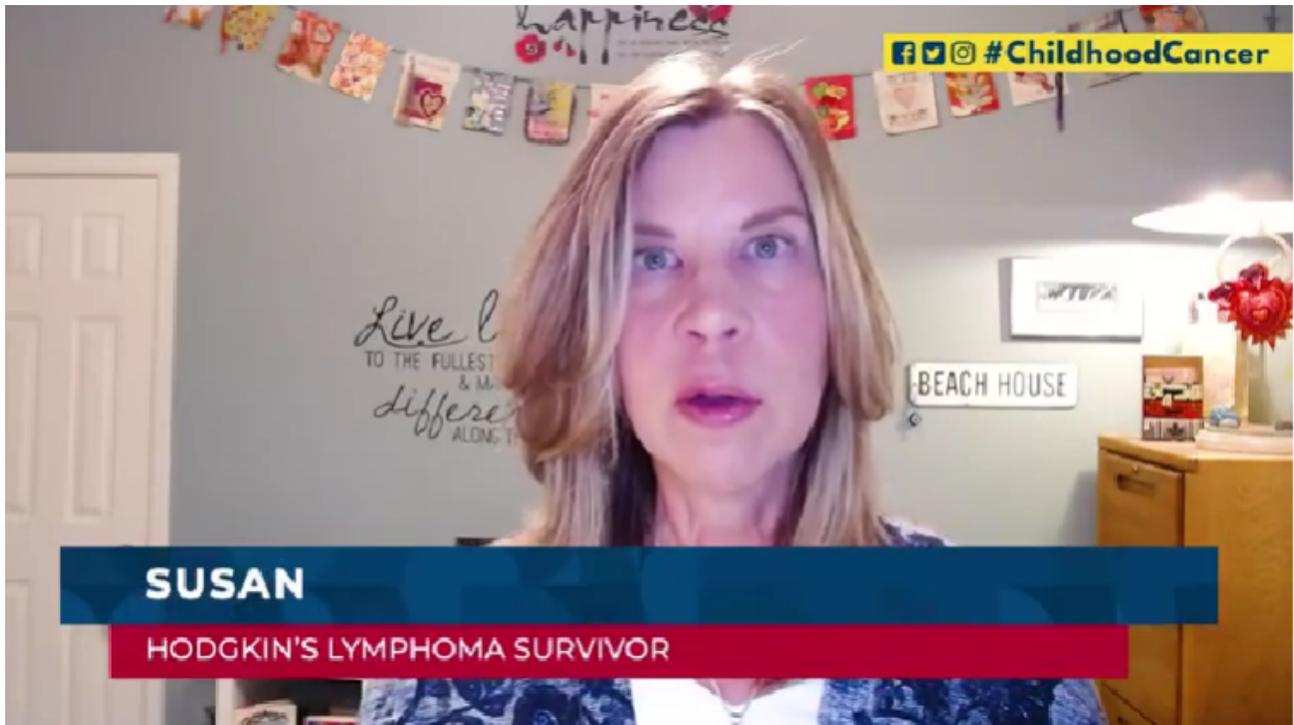
The PFDD process allows patients' voices to inform the development of a benefit-risk framework for use in the evaluation of new treatments, as well as provide important perspective for health care providers. Pediatric cancer survivors living with cardiac late effects have a unique perspective on the dimensions that are most important and critical to regulatory decision making, the unmet medical needs of others with these late effects, and the benefit-risk tradeoffs that may be acceptable across the continuum of their conditions. Armed with the insights from survivors and caregivers, drug developers should be better able to design clinical trials to assess outcomes that are clinically meaningful, address aspects of disease that are most critical to people living with the disease and, hopefully, achieve a higher chance of success.

Defining benefit expectations and risk tolerance among people with cardiac late effects when considering various treatment options should enable better characterization of tradeoff decisions faced by patients, families, and healthcare providers, as well as regulators.

There needs to be even greater incorporation of the survivor and caregiver voice in drug development to prevent, mitigate, or improve treatment for these late effects. This perspective should inform those developing drugs to treat pediatric cancers by considering long term effects as early as possible in the design of their therapy development programs and may assist the FDA in using patient experiences when evaluating products for marketing approval, including evaluating the benefit-risk of new treatments.

Specifically, clinical investigators should incorporate more **patient-centered endpoints** for cancer clinical trials and cardiac late effect clinical trials by identifying, collecting, measuring, and considering meaningful experiences of patients, survivors, and caregivers. Pediatric cancer clinical research should further efforts to focus on **designing clinical trials** that emphasize long term safety just as they focus on efficacy in treating the cancer.





SUSAN

HODGKIN'S LYMPHOMA SURVIVOR

"The treatments that saved my life now seem to be slowly stealing it, and on difficult days, I feel as if survivorship is a progressive terminal illness."



Cardiac Late Effects EL-PFDD Meeting Design

The **Food and Drug Administration (FDA)** is tasked with protecting the public health by ensuring that drugs, vaccines, biological products, and medical devices intended for human use are safe and effective.

To enhance its ability to obtain the **patient perspective on specific diseases** and their treatments, the FDA has conducted disease-specific patient-focused drug development (PFDD) meetings and has welcomed patient organizations to conduct Externally-led PFDD (EL-PFDD) meetings. Background and guidance on EL-PFDD meetings can be found at this link: <https://www.fda.gov/industry/prescription-drug-user-fee-amendments/externally-led-patient-focused-drug-development-meetings>.

In May 2021, Children's Cancer Cause submitted a letter of intent to the FDA to commence the process of leading an EL-PFDD, with the support of other partner organizations including the American Academy of Pediatrics, American Society of Clinical Oncology, American Society of Pediatric Hematology/Oncology, The Andrew McDonough B+ Foundation, and Teen Cancer America, who provided expertise on the meeting content and provided extensive outreach to help engage and mobilize their constituents in raising awareness about the meeting and the need for better understanding the patient perspective around cardiac late effects.

Held during the 10th anniversary year of the PFDD program, this meeting on September 15, 2022, became the 74th EL-PFDD meeting and the 35th to be held virtually (due to the ongoing COVID-19 pandemic). This event enabled members of the pediatric cancer survivor community to share information about the **burdens of the condition and perspectives on future treatments**.

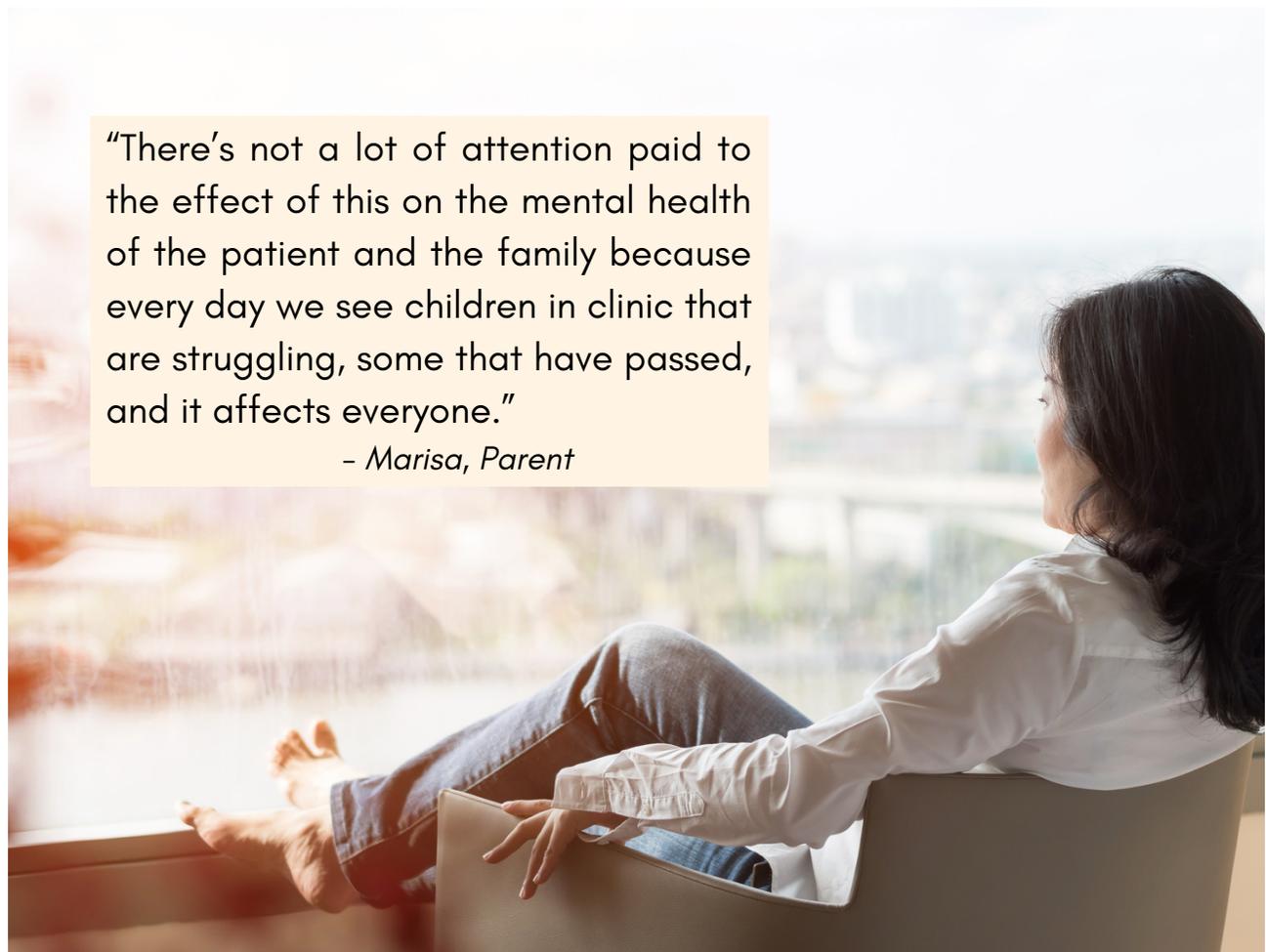
The goal was to provide input to support FDA, medical product developers, health care providers, researchers, and other key stakeholders' understanding of the **severity** of the condition, the **urgency** of current complex and unmet medical needs for patients, and the **importance** of future consideration of novel treatment options.

The meeting was designed to bring together diverse members of the childhood cancer stakeholder community of patients, survivors, family members, partner patient advocacy groups, academic investigators, clinicians, industry partners, and government agency colleagues to gain a deeper understanding of the **symptoms and burdens of cardiac late effects in daily life**, as well as the **medical and psychosocial needs** of this community.

The voices of pediatric cancer survivors and caregivers impacted by cardiac late effects were heard through their testimonials, live polling of the broader audience, open discussions with meeting attendees, and post-meeting surveys. The EL-PFDD meeting was held via livestream webcast and attended by approximately 150 registrants representing a variety of stakeholders.

The meeting was moderated by James Valentine, JD, MHS, of Hyman, Phelps & McNamara, who has led many EL-PFDD meetings and previously worked at the FDA, where he helped launch the PFDD program. The meeting consisted of two panel sessions, with patients and caregivers providing testimonials and engaging in facilitated discussion. Participants had the opportunity to contribute by submitting written comments and calling in, as well as responding to live-polling questions. In the 30 days after the meeting, individuals had the opportunity to review the recording and submit additional written comments as well as respond to a post-meeting survey.

A recording of the entire EL-PFDD meeting is permanently available at www.childhoodcancerpfdd.org, a Children's Cancer Cause website devoted exclusively to childhood cancer-related PFDD meetings.



"There's not a lot of attention paid to the effect of this on the mental health of the patient and the family because every day we see children in clinic that are struggling, some that have passed, and it affects everyone."

- Marisa, Parent

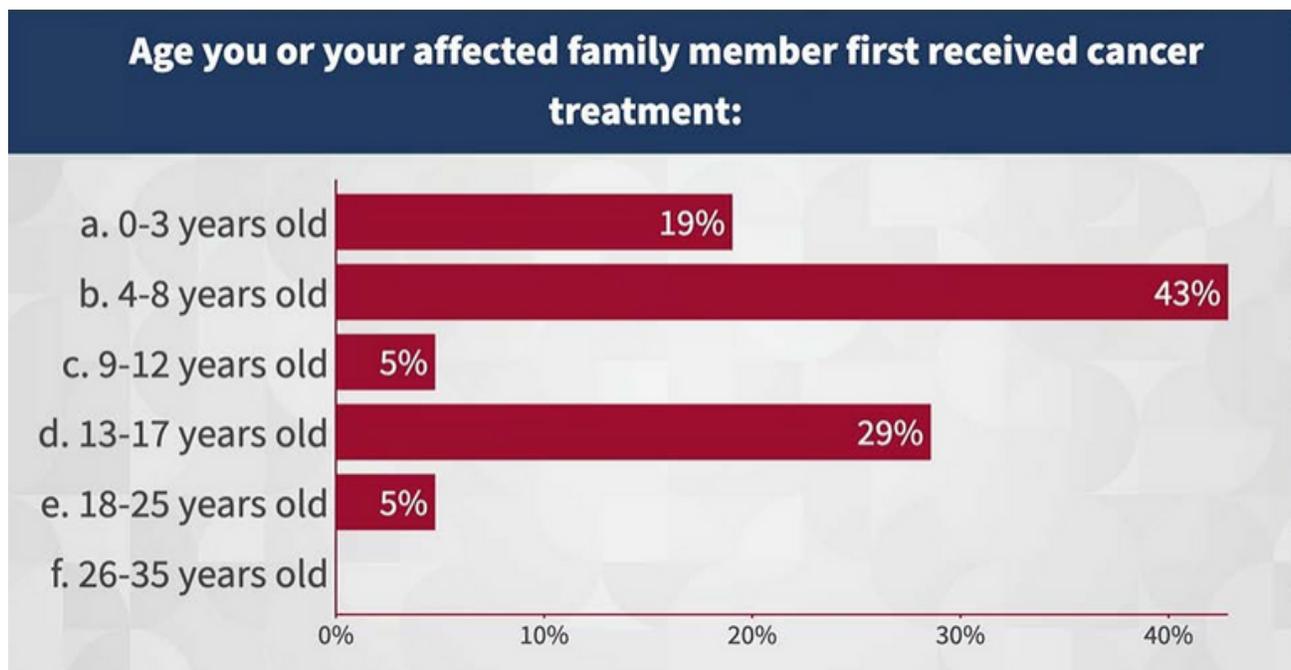
Meeting Participant Demographics

Instant polling questions were used to identify the demographics of the livestream audience for the meeting.

At the outset of the meeting, **half of all responding participants self-identified as a person living with treatment-induced cardiotoxicities**, while 35% indicated they were caregivers of someone living with treatment-induced cardiotoxicities. The remaining 15% were split between patients at risk for such late effects and their caregivers.



Of the majority (77%) of responses that indicated experience with cardiac late effects, 42% were at least 11 years out from finishing cancer treatment (21% of responses were 11-14 years and 21% were 15-25 years since that time). A smaller percentage, 8% and 4%, indicated cancer treatment had concluded more recently (6-10 years and 1-5 years ago, respectively). Thirteen percent of responses indicated completing cancer treatment but no experience with cardiac late effects.



Report Overview

This Voice of the Patient (VoP) Report summarizes the perspectives shared by survivors and caregivers at the EL-PFDD meeting, including responses/results from panelists and people who called or wrote in. The terms and language used in this report to describe cardiac late effects, including its symptoms, impacts, treatment experiences, and priorities for future treatments, reflect those used by meeting participants.

Pictured on this page are during-treatment photos of survivors who participated in the meeting.



This report intends to support and enhance FDA, medical product developers, health care providers, researchers, and other key stakeholders' understanding of:

- The symptoms and burden of living with cardiac late effects on pediatric cancer survivors and their caregivers
- Perspectives on the treatments and approaches currently used to manage the condition
- Survivor and caregiver aspirations and what is important to them for future treatments

By describing the survivor experience with cardiac late effects, this document highlights the serious nature of the condition and the **significant existing gaps in meeting the needs** of patients and caregivers. It is hoped this report will lead to greater incorporation of the survivor voice in drug development to prevent, mitigate, or improve treatment for these late effects. The goal is to inform sponsors on the design of their therapy development programs and assist the FDA in using patient experiences when evaluating products for marketing approval, including **evaluating the benefit-risk of new treatments**. Specifically, information in this report can help inform sponsors, clinical investigators, and the FDA about patient-centered endpoints for cancer clinical trials and cardiac late effect clinical trials by identifying, collecting, measuring, and considering meaningful experiences of patients, survivors, and caregivers.



In this report, pediatric cancer survivors and caregivers are collectively referred to as “participants.” We use the term survivor instead of “patient” in this report, as these individuals have survived pediatric cancer (though they are patients due to their experience with cardiac late effects). We use the term “caregiver” to refer to a family member, partner or friend who provides (or did provide) direct care for the patient.



FDA Perspective

"I can assure you that we are here to listen and to learn. You all have much to teach, and I hope that this meeting has the impact that you deserve."

- Gregory Reaman, MD

FDA staff with expertise relevant to the meeting topic attended the EL-PFDD. Gregory Reaman, MD, formerly of the Oncology Center of Excellence (OCE) within the Center for Drug Evaluation and Review (CDER), provided opening remarks.

In his comments, Dr. Reaman emphasized that hearing directly from patients, survivors, and their caregivers about what is most important in treatment or management of cardiac late effects through the EL-PFDD format provides the FDA with a clearer picture of how to evaluate potential new therapies.

Dr. Reaman noted the excitement about significant progress in improving the outcomes for children with cancer by changing a previously uniformly fatal disease to one in which most children experience prolonged survival, and many are even cured. He stressed, however, that this excitement is dampened by the realization of the burden and the cost of treatment and diminished quality of life experienced by patients and families. **Dr. Reaman acknowledged that as more people survive childhood cancer, a growing number experience life-altering and even life-threatening conditions from the side effects of effective therapy.** Dr. Reaman described a 10-fold increase in stroke and coronary artery disease and a 15-fold increase in heart failure experienced by childhood cancer survivors as compared with their healthy siblings. Current treatments for these medical conditions may not be appropriate for long-term childhood cancer survivors and are currently only approved for use in adults.

As cardiotoxicity has emerged as one of the most concerning late effects, pediatric cancer clinical research is transforming to focus on designing clinical trials of new agents that emphasize long term safety as equal in importance to efficacy in treating the cancer.

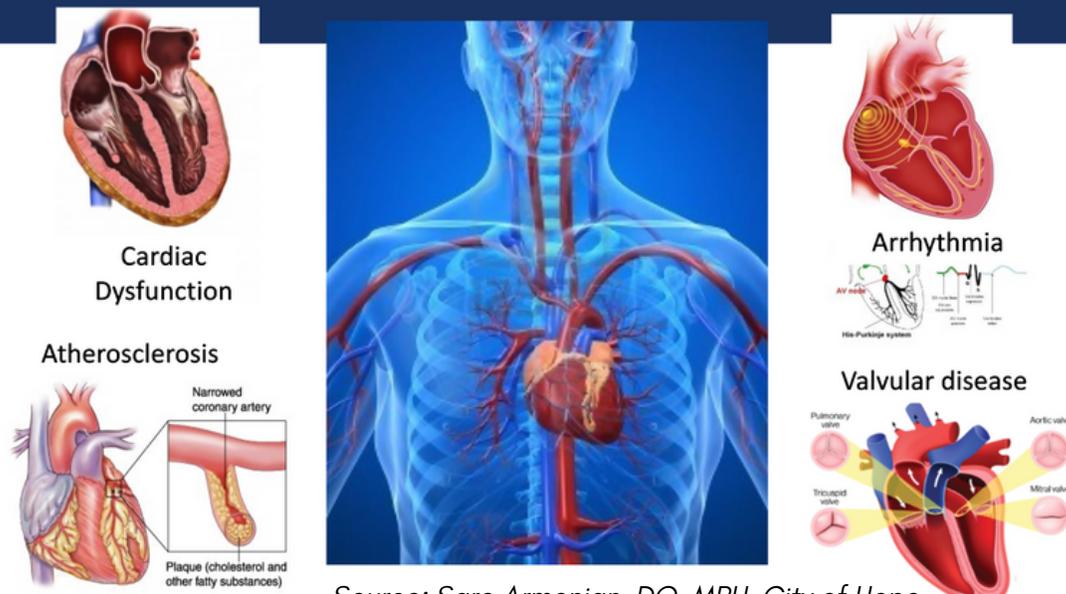
Dr. Reaman stressed that FDA colleagues from oncology, cardiology, and nephrology were all tuning into the PFDD meeting to gain insights from participants' experiences that will inform regulatory review and decision making moving forward. While analysis of quantitative safety or toxicity data available from clinical trials is critical to FDA decision making, the qualitative reporting of real-life patient experiences provides important additional context.

Overview of Cardiac Late Effects

Two clinical presentations offered PFDD participants an overview of the causes and risks associated with cardiac late effects for pediatric cancer patients, as well as opportunities for improving outcomes for these individuals.

Overview of Cardiac Late Effects Among Pediatric Cancer Patients

Cardiovascular diseases in cancer survivors



Source: Saro Armenian, DO, MPH, City of Hope

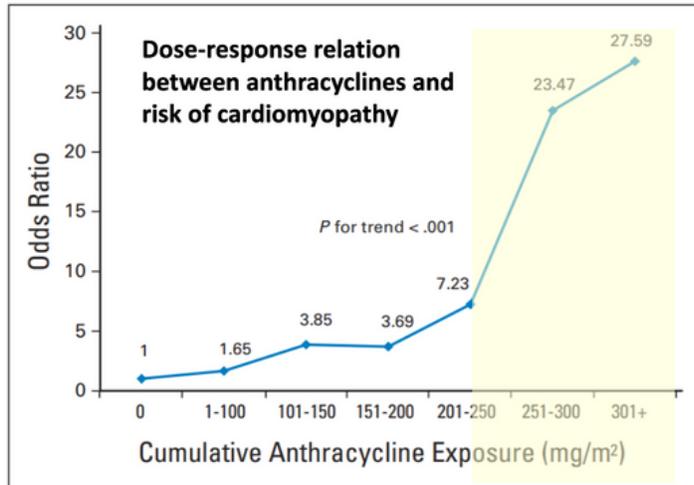
Dr. Smita Bhatia, from the University of Alabama at Birmingham, provided a clinical overview of the **causes and symptoms** of cardiac late effects among pediatric cancer survivors, focusing on how cancer treatment causes cellular damage in the heart muscle or the blood vessels that supply the heart. She described how **cardiomyopathy** develops and progresses, especially among patients exposed to treatments commonly used for childhood cancer that include **anthracyclines**. Cardiomyopathy is a disease of the heart muscle that makes it harder for the heart to pump blood to the rest of the body.

Dr. Bhatia described the strong relationship between cumulative exposure to anthracyclines and the risk of cardiomyopathy. Anthracyclines cause damage to heart muscle cells, leading to scarring that can eventually cause **heart failure**. While there is variability among individuals in terms of their susceptibility to anthracycline-induced heart damage, about 60% of children exposed to high-dose anthracyclines demonstrate abnormal changes in their **cardiac function** on echocardiogram exams. **As the dose of anthracycline increases, so does the risk of serious cardiac damage and death.**

Cardiomyopathy

Anthracycline-Related Cardiomyopathy After Childhood Cancer: Role of Polymorphisms in Carbonyl Reductase Genes—A Report From the Children's Oncology Group
 Joseph H. Blumer, Alan H. Hsiao, Wendy Landier, Lu Shen, Diego Argente, Sheng Wang, Jannong Allen Mao, Debra J. Friedman, Ed P. Giordano, Melissa M. Stauden, Joseph P. Nagler, Kristin C. DeRubeis, & Kim Raskin, Christopher Villaluna, Mary V. Bellizzi, and James Blume

J Clin Oncol, 2012;30:1415-21

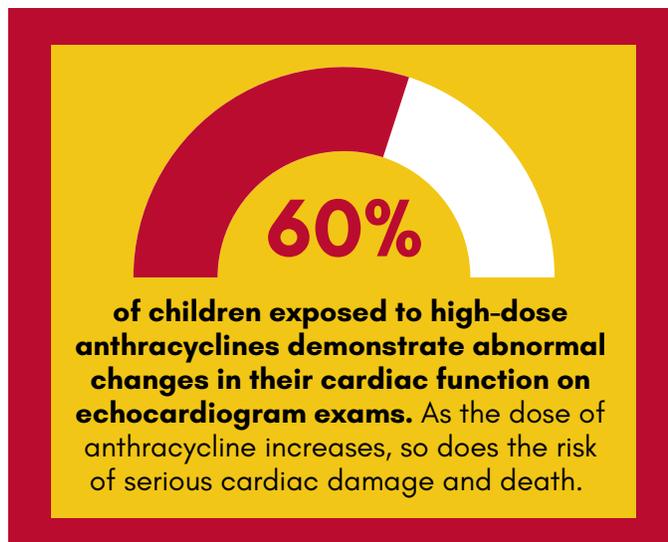


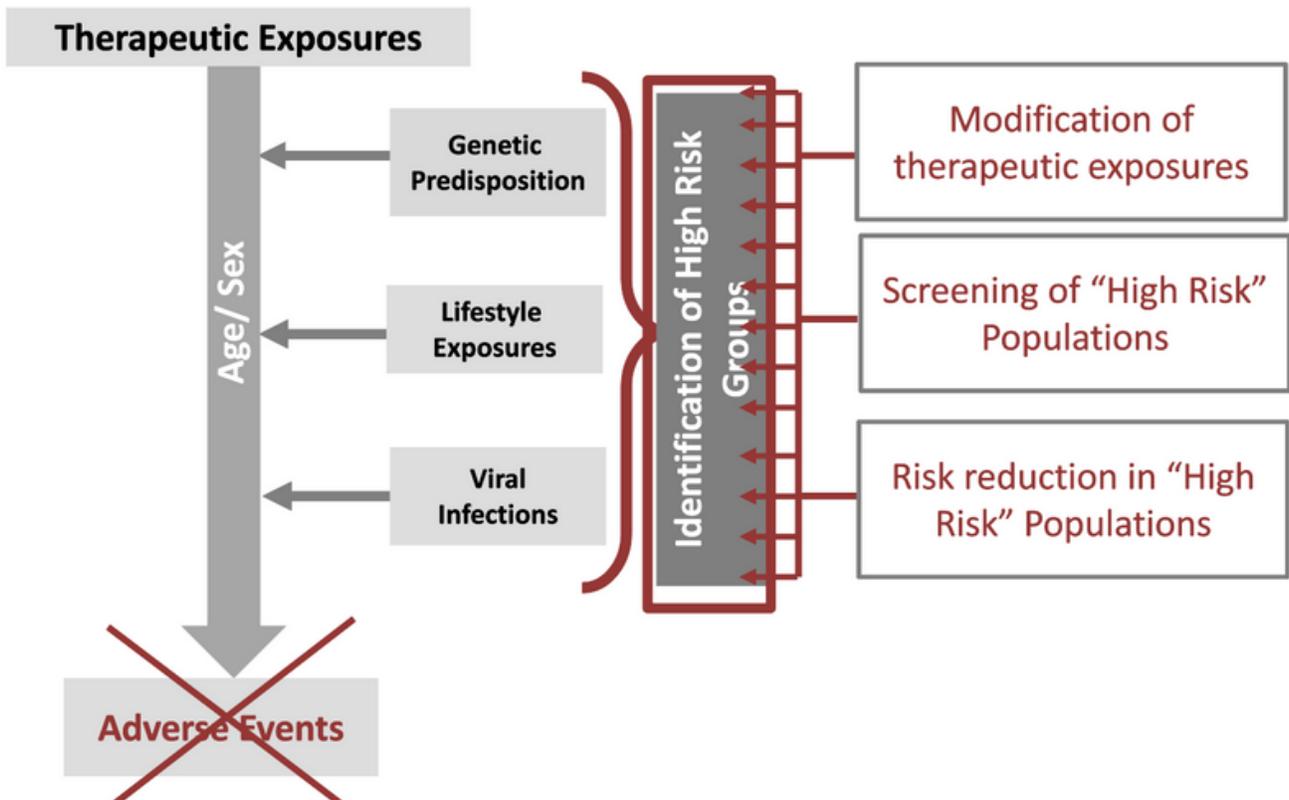
~60% of children exposed to high-dose (≥250 mg/m²) anthracyclines demonstrate echocardiographic indices of abnormal cardiac remodeling
Circulation. 2013;128:1927-95

Prognosis
 5-year survival rates of less than 50%
N Engl J Med.2000;342:1077-84

Source: Smita Bhatia, MD, MPH, University of Alabama at Birmingham School of Medicine

Ongoing research is attempting to better define patients at **higher risk** of cardiac late effects caused by anthracycline exposure. Dr. Bhatia is among a cadre of experts conducting studies to identify certain genes associated with a higher likelihood of developing cardiomyopathy. The hope is that differentiating among sub-populations with various demographic factors will identify and allow for proactive management of individuals at highest risk of serious cardiac late effects. Combining information about genetic predisposition, presence of other cardiovascular **risk factors, diabetes, hypertension, and viral infections** can help clinicians develop an overall picture of an individual's risk of developing cardiomyopathy. Such information is important as many of these risk factors impact non-white populations at higher rates than whites. In this way, it may be possible to modify anthracycline dosage and exposure, to determine how often patients should be screened with echocardiograms or other **cardiac monitoring** approaches and learn how aggressive to be with implementing other heart failure risk reduction protocols.

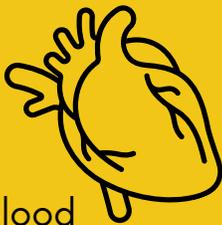




Source: Smita Bhatia, MD, MPH, University of Alabama at Birmingham School of Medicine

Cardiomyopathy:

a disease of the heart muscle that makes it harder for the heart to pump blood to the rest of the body.



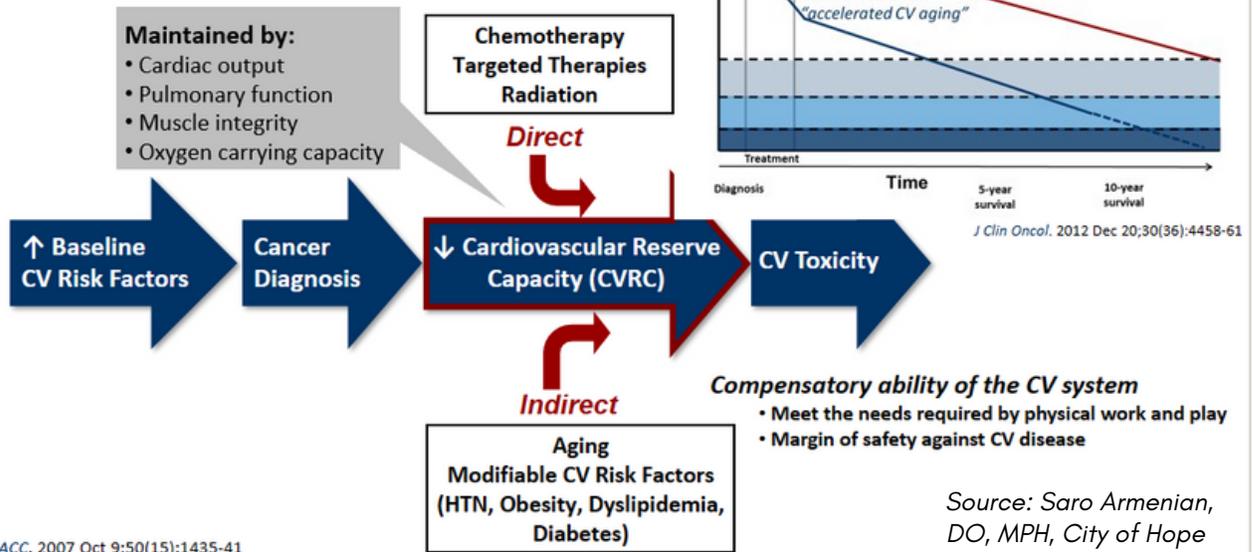
Dr. Saro Armenian (pictured below) from City of Hope Comprehensive Cancer Center in California provided a clinical overview of current and future treatment options for cardiac late effects, noting that most cancer treatments (including novel immunotherapies) carry some risk of cardiovascular side effects. He stressed the importance of understanding the risks and **potential mitigation strategies** for pediatric cancer survivors by learning from what is happening in adult patients.

Among cancer survivors, the normal cardiovascular reserves are depleted more rapidly – this often occurs decades earlier than in the general population. In fact, the combined exposure to anthracyclines and hypertension puts survivors at greater than 30 times the risk of developing heart failure before individuals who would regularly be screened for cardiac risk factors (e.g., hypertension) but who have not been exposed.



Nature of the problem:

The 'Multiple-Hit' Hypothesis



Dr. Armenian emphasized how these realities point to the urgent need for a holistic approach to pediatric cancer survivorship care, moving beyond an annual visit to **long term follow-up care in real time**, using **new technologies** to monitor key vital signs and support healthy behaviors (e.g., routine exercise, diet, etc.). Additionally, **early screening** and monitoring for cardiac disease with echocardiograms or other emerging cardiac imaging technologies are vital, and there are ongoing efforts to adopt remote patient monitoring, using affordable and portable cardiac monitoring devices.

Evolving Patterns of Healthcare Delivery

Traditional paternalistic model of care



- Patient completely reliant on HCP to receive information, diagnosis and referral
- Difficult for patients to navigate within and between health and social care
- Interventions usually in response to physical evidence

Empowered patient sharing ownership



- Patient informed whenever and wherever, using their interoperable medical record
- Co-creation of care packages, proactive prevention, rapid access to services
- Technology enabled support and self-management

Source: Saro Armenian, DO, MPH, City of Hope

Finally, Dr. Armenian summarized approaches to treatment of cardiac late effects. Treatment considerations should begin before cardiotoxic therapies are given, considering alternatives that may be less toxic or planning for early screening and intervention and **proactive management** of cardiovascular risk factors. This management occurs through **multidisciplinary, multi-institutional collaborations and incorporation of technology and mobile options** to ensure that all patients are followed appropriately.

Take home messages

Source: Saro Armenian,
DO, MPH, City of Hope

- Advances in cancer treatment and supportive care require ongoing long-term vigilance for late cardiovascular disease in aging childhood cancer survivors
- Pre-cancer treatment prevention is the most effective strategy for chronic disease risk reduction
- Early screening for cardiovascular late effects necessary for certain cancers where cardiotoxic therapies remain necessary for cure
- Multi-institutional, -disciplinary, collaborations are necessary for successful implementation
- Considerations:
 - Highly mobile survivor population
 - Transition of care (pediatric to adult; cancer to primary care)
 - Advances in technology to bridge the gap



“After relapse in 2010, I qualified for [a] clinical trial, which saved my heart from further damage in preparation for my stem cell transplant. This trial allowed me to go into transplant a little more whole.”

–Sarah, Survivor

Key Themes

Throughout the EL-PFDD meeting, multiple key themes and shared experiences emerged relating to areas of unmet need for pediatric cancer survivors impacted by cardiac late effects. While most expressed a sense of gratitude for having survived cancer, they also described a **lack of information** to prepare for the future. They expressed feeling that there were no good choices, and that the disappointment and frustration that the same treatments used to beat back the cancer were responsible for causing **serious persistent new health problems that worsen over their lifetime.**

Survivors and caregivers spoke emphatically about **feeling betrayed** by their experience. While they expressed appreciation for the treatment benefit of longer life, they also described the double trauma caused by suffering from serious life-threatening **health conditions resulting from that treatment.**

For many parents of pediatric cancer survivors, this trauma is compounded by feelings of **guilt and anxiety**, as they lament the difficulty of making the decision to allow critically important cancer treatments to be given, at the same time worrying about how late effects of treatment will affect their children's futures.

“There are myriad, millions and billions of concerns for the future. Is there something we can do to help these kids live stronger, better lives, without having the constant worry of mortality at a very young age, because of a medication they needed early on?” - *Tina, Parent*

“It has not been easy. It’s been a long 50 years of struggling with different issues, but I am completely grateful for the time that I’ve had. It was 45 years more than I was totally going to have.” - *Erin, Survivor*

“The treatments that were saving [my daughter’s life] were now compromising her life.” - *Patty, Bereaved Parent*

“Parents hold a very heavy burden on whether they made the best decisions on treatment, especially when serious lifelong effects are being experienced, like heart issues.” - *Charlene, Parent*

Living with Cardiac Late Effects

**"[T]he effects of childhood cancer last a
lifetime, and survival comes at a great cost."**

- Susan, Survivor

Meeting Discussion Topic 1: Living with Cardiac Late Effects

The morning session of the EL-PFDD meeting was focused on hearing from survivors and caregivers about what it is like to live with cardiac late effects after pediatric cancer treatment. Five panelists – two cancer survivors and three caregivers – presented brief descriptions of their experiences, describing symptoms and the impact of cardiac late effects on their lives. *Full statements from each panelist can be found in [Appendix 3](#).*



Susan is a Hodgkin's lymphoma survivor, treated at 17.

Susan has been dealing with late effects for decades. She required a heart valve replacement in her 40s and was diagnosed with breast cancer two years later. She said, “[T]he effects of childhood cancer last a lifetime, and survival comes at a great cost.”



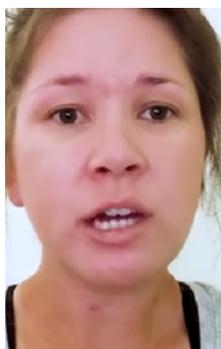
Charlene is mom to Ruth, who was treated for stage 4 neuroblastoma at age 5.

Ruth, now 20, has had a variety of cardiac late effects including cardiomyopathy and decreased lung function, and she uses portable oxygen and needs a wheelchair for longer trips. These cardiac issues have affected every part of her life and pose many challenges as a young adult that are preventing her from living a full and independent life.



Lynn is mom to Peyton, who had embryonal liver sarcoma.

There was only one chemotherapy treatment option. Peyton, now 17, is regularly screened for cardiac late effects. Lynn is plagued with worry as her daughter gets older. Lynn shared, “[C]ancer is a restless and relentless disease that affects the mental and physical health of my daughter and our entire family for a lifetime.”



Kelsey is 29 and had juvenile myelomonocytic leukemia at age 3.

She has gradually experienced chest pain, tachycardia (rapid heart rate), and hypertension. Tachycardia affects exercising, playing sports and activities. She stated, “[D]octors say ‘we don’t know what’s wrong with you’ and there is this looming dark cloud over you that there’s a possibility that things are heading for the worst and (just) that (alone) is the worst feeling in the world.”

Patty's daughter Abby had leukemia at age four and was treated with doxorubicin (an anthracycline). She eventually developed chemo-related cardiomyopathy and rapidly declined, needing home nursing care for years. She was exhausted, slept often, had GI difficulties, pain, kidney issues, and lost mobility. Abby could not do anything a child of her age usually does and was home schooled.



Abby was not eligible for a heart transplant and, at age 15, had a left ventricular assist device implanted but never woke up and died from a post-operative stroke.

"My daughter's life ended due to cardiac long-term effects, and she ran out of treatment options."

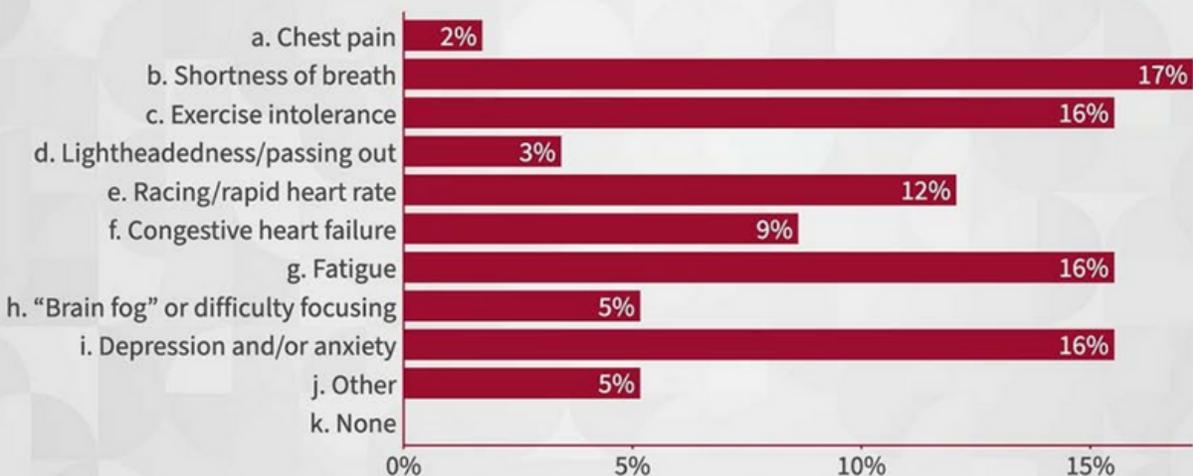


After the panelists spoke, a live Zoom panel of survivors and caregivers gave comments, followed by meeting participants being led through a moderated discussion with live polling questions and the opportunity to call-in or submit written comments. Zoom panelists were able to share their experiences and perspective based on the polling and comments shared by other meeting participants.

Polling: Most Significant Health Impacts

Participants were given nine specific symptoms to choose from and were invited to select the top three most significant health impacts they face due to cardiac late effects. Respondents also had the option to select other or none. The top four symptoms selected were **shortness of breath, exercise intolerance, fatigue, and depression**. Racing/rapid heart rate and congestive heart failure were the next most frequently selected.

What are the health issues that impacted you or your affected family member most? (Select top THREE)



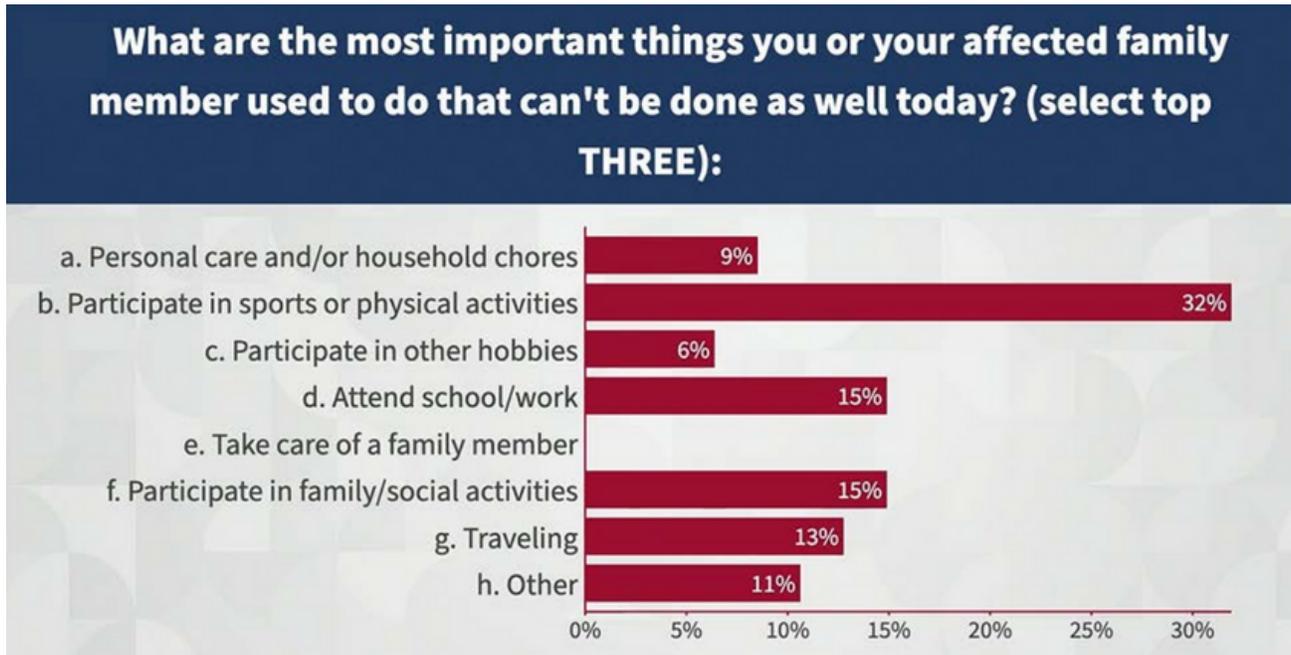
"I was still doing marathons and noticed I was getting progressively slower... I was surprised by that because it crept up on me. By the time I went to see a doctor, I had severe aortic stenosis."

- Erin, Survivor



Poll: Impact of Cardiac Late Effects on Daily Life

When asked to select the **top three most important aspects of daily life** that are impacted by cardiac late effects, **the ability to participate in sports or physical activities** was the top selection (by 32% of respondents), followed by *attend school/work, participate in family/social activities, and traveling*.



PFDD participants were also asked to select their **top three worries** related to heart disease in the future, choosing from among 10 specific options and other.

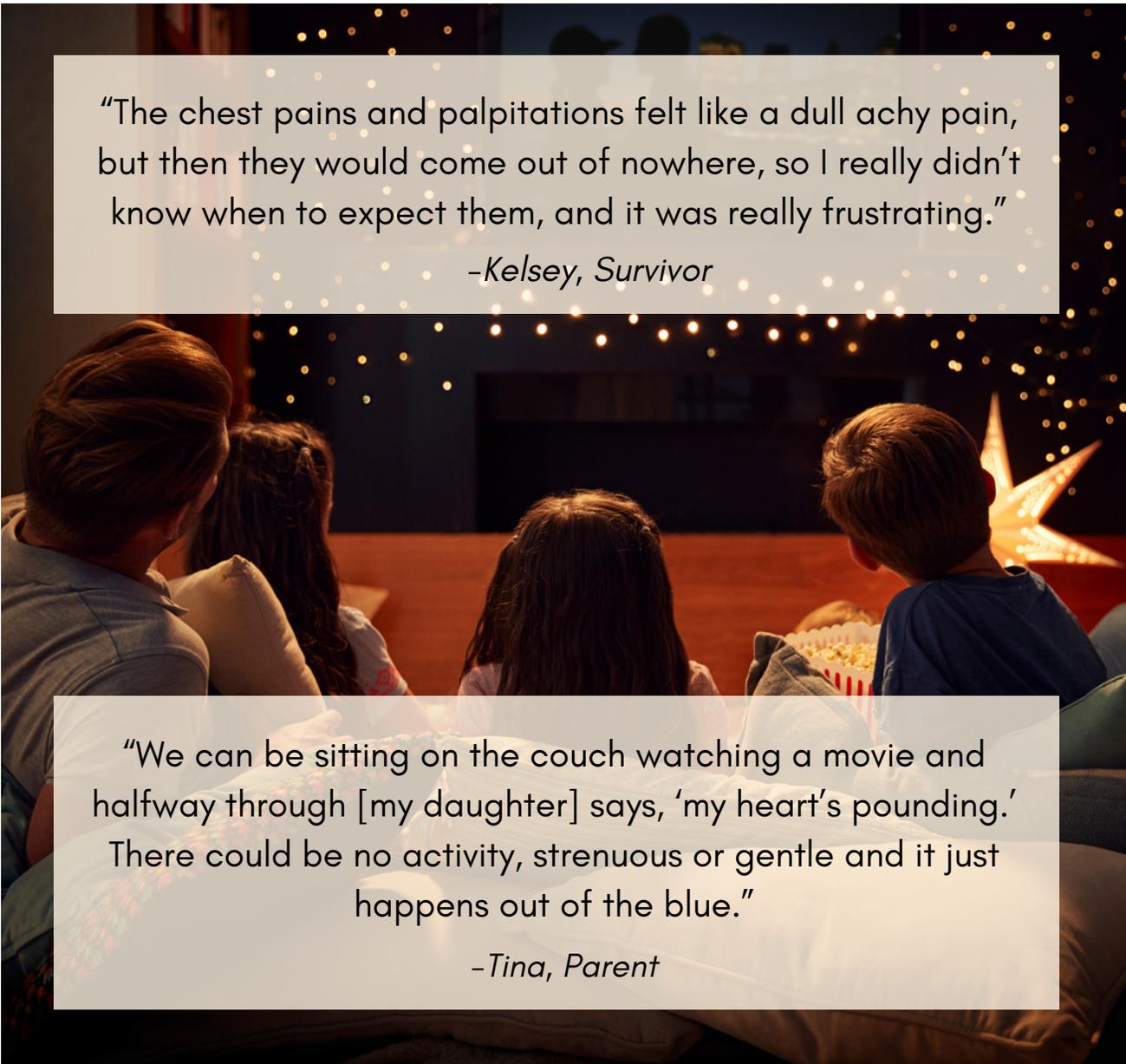
The number-one response was needing heart surgery/heart transplant.



Impacts of Cardiac Late Effects on Daily Life: **Voices of Survivors and Caregivers**

The following selection of survivor and caregiver comments reflects the primary symptoms and impacts on daily life that were discussed by meeting participants.

Individuals living with these late effects and their families face a wide range of significant physical, emotional, quality of life, and logistical burdens due to cardiac late effects. Survivors described their struggles with regular chest pain and feeling like their hearts are racing, even when they are just sitting still. These situations provoke tremendous anxiety and frustration, especially since they often occur without warning.



“The chest pains and palpitations felt like a dull achy pain, but then they would come out of nowhere, so I really didn’t know when to expect them, and it was really frustrating.”

-Kelsey, Survivor

“We can be sitting on the couch watching a movie and halfway through [my daughter] says, ‘my heart’s pounding.’ There could be no activity, strenuous or gentle and it just happens out of the blue.”

-Tina, Parent

Physical Impacts

Cardiac late effects tend to worsen over time, potentially leading to serious chronic and life-threatening conditions, including heart valve disease (such as aortic stenosis), cardiomyopathy, heart failure, or a heart attack. Survivors and caregivers described their efforts to come to terms with and manage these conditions, while **cop**ing with the idea that they may not survive a **severe cardiac event**.

“With the onset of [my son’s puberty] ... we were dealt a new list of additional side effects, cardiomyopathy being one of them. That’s an awful lot for a young tweener, emerging teenager to have to deal with.” - *Mary Beth, Parent*

“My primary concerns are that of heart valve disease, a heart incident, my mortality.” - *Angela, Survivor*

“My continued concern is that even though I had the heart transplant, that now I am still [able] to see my own mortality, because heart transplants don’t last forever. They do have an expiration. So, I continue to deal with mortality issues as being a young cancer survivor... Even though I am living my best life, thinking something could happen always worries me.” - *Jarvis, Survivor*

“My cardiologist told me I am a walking cardiac event, which is scary to hear but it’s reality, and I take a lot of medicine daily just to maintain my ability to function.”
- *Greg, Survivor*

Meeting participants also detailed their experiences with **shortness of breath** and periods of **extreme fatigue**, along with **significant weight loss**.

“I have to recognize that when I’m tired, I need a nap. There could be something else. Be careful of putting in a level of effort that might seem average to the average person my age, because I’m not average with the health experiences that I’ve been through. It’s like I have to think before I do.” - *Angela, Survivor*

“Something as simple as climbing the stairs to get from the main floor of our house to [my daughter’s] bedroom causes her to stop and have to take a breath by the time she gets to the top, before she can continue her journey around the corner to her bedroom.”
- *Tina, Parent*

Quality of Life Impacts

Meeting participants detailed the extent to which ongoing healthcare activities are central to their lives as they must travel away from family and normal daily life to see multiple providers and specialists for their various cardiac conditions. **Heart concerns are always front and center** in these individuals' minds as they continuously monitor the functions of their heart and how they are feeling.

"My daughter's care required frequent trips to the doctor and inpatient stays, with thousands of nights in the hospital, often in intensive care. She often required air transport to a hospital that could support her cardiology needs."

- *Patty, Parent*

"Traveling more than an hour each way to see various specialists has become a way of life."

- *Susan, Survivor*

"I constantly have to check my heart rate and also my oxygen concentration. . . [I]'s just been a huge balancing act. There are things that have worked really well, which is like staying on oxygen and keeping up with my heart medications and keeping up with my doctor's appointments and having a really great team."

- *Ruth, Survivor*

Many women who survived pediatric cancer only to face cardiac late effects were eventually **advised not to get pregnant** due to the strain on their heart function. This is a devastating quality of life consequence for participants, who described the difficult set of decisions and **trade-offs** they were forced to make.

"The function of her heart and lungs affects her outlook on the future, like marriage, having a child, living on her own as an adult, and supporting herself. It is a constant balancing act to live with decreased heart function and transitioning to adult care."

- *Charlene, Parent*

"I renounced to be a mother for the huge fear of putting my body under stress and danger again. Knowing that I developed breast cancer, anyway, broke further my heart since I feel I have renounced something important to avoid side effects that have come anyway. It's heart breaking."

- *Elisa, Survivor (Written Comment)*

"One of the big [things] that has been really hard to accept is carrying a child... I always wanted to be a mother. Unfortunately, after going to multiple different doctors and really talking about the nitty-gritty of how I would be a high-risk pregnancy due to my cardiac late effects, they left it up to me. They didn't recommend it, obviously..." - *Sarah, Survivor*

Quality of Life Impacts, continued

Meeting participants also described how shortness of breath, breathing difficulties, and extreme fatigue associated with cardiac late effects **impact their ability to remain engaged with peers** in physical and social activities as well as making it much more difficult to live their lives to the fullest.



"I'm a 39-year Hodgkin lymphoma survivor. I've lived in Colorado for 30 years, but I'm finding that living at altitude is difficult because of cardiac and pulmonary late effects. I'm now on supplemental oxygen at night. As I'm aging, I need to move out of state to sea level to lessen the stress on my heart and lungs. This means moving away from my support system to someplace unfamiliar."

- Susan, Survivor (Written Comment)

"As I went into later adulthood, I could definitely feel that I [could] not walk a long distance without stopping, taking a breath, or resting. I had a hard time keeping up with my friends."

- Jarvis, Survivor

"Fatigue [impacts my] ability to do certain activities of daily living, like I can no longer really comfortably bend down as much as I would like to if I drop something on the floor.

I also feel like I can't really do laundry anymore."

- Jacob, Survivor

Mental and Emotional Impacts

"Aging as a survivor of pediatric cancer is terrifying."

- Susan, Survivor

Along with the significant physical and quality of life impacts of cardiac late effects, participants also described a common set of mental and emotional impacts relating to feelings of anxiety and fear. Survivors and their caregivers express a **deep concern about the future**, with a sense that a significant cardiac event could happen at any moment. Carrying around the knowledge that their heart function is damaged creates an enormous burden on the psyches of individuals who have cardiac late effects.

"My mental health has become as important as my physical health to me, they are unavoidably linked." - Megan, Survivor

"People have no idea of the **late effect ticking time bomb** [inside my daughter]... [she] harbors intense anxiety about her body. Not the typical teenage stuff like 'does my hair look okay,' [but] deep, hidden, and isolating fear." - Lynn, Parent

"About a year after my surgery, I realized I was **devastatingly depressed**. After all that I have gone through and continue to go through, I started thinking it would be easier to throw myself in front of a train. I started seeing a psychiatrist for my major depressive disorder and unrealized general anxiety disorder and I started talk therapy." - Megan, Survivor

"I worry about [needing more surgery]. I think anybody would worry about that and it's just hopefully never a heart transplant but that's something that may happen, and cross that bridge when you come to it. [In] terms of dealing with it, I think it's trying not to let the possibility of those difficult obstacles totally sidetrack your daily life." - Greg, Survivor

"Sometimes I look on the calendar and it's a countdown to [my daughter's] next Echo, because I'm nervous about what I can't see and her daily routines and activities, and I'm always watching. The questions are always there. **The constant vigilance never ends.**" - Tina, Parent

"It's this **dark cloud** looming over you, that there's a possibility that things are heading for the worst, and just that alone is the worst feeling in the world." - Kelsey, Survivor

"[It was] very frightening that at 14 years old, my son was diagnosed with cardiomyopathy at the same time that my 75-year-old father was dealing with a lot of heart issues. [My son] saw himself in the mirror of a 75-year-old man." - Mary Beth, Parent

Mental and Emotional Impacts, continued

Feelings of social isolation are common among pediatric cancer survivors dealing with cardiac late effects, as the physical and mental impacts of ongoing health issues force them to opt out of aspects of their normally busy lives and regular interactions with friends, families, and peers.

“Our children, as they transition to adults, they’re people first. They need their friends; they need their family. As long as quality of life allows them to be with them, they’re getting important support. It’s when quality of life forces them to stay at home, or worse in bed that they are really isolated. And those are the moments when they really, really struggle.”

– Mary Beth, Parent

Survivors and families described the extent to which they struggle with the emotional impact of **feeling ill-prepared** for what may come in terms of cardiac late effects. During the meeting, many described their **dismay about how little communication and information** they received from their cancer physicians and healthcare providers about what to expect from future cardiac issues. They also detailed the emotional turmoil caused by **feeling like they had no choice** but to pursue a highly toxic therapy to defeat the cancer, rather than having options to choose a treatment option with fewer side effects.

“You’re not told anything about what to do or what to look for or what to expect past a certain point in [cancer] treatment... We don’t have a doctor that we can consult that knows enough about progression [of cardiac late effects]. Everything that I’ve been doing and all of the experts in all of the reading that I’ve been managing is really on my own.” – Marisa, Parent

“If the only other option is death, then we need more options.” – Sarah, Survivor

“It was bad enough that my child was going to be given one of the harshest chemotherapies to save her life at age 10, but those same drugs might kill her at 20, 30, 40 years of age. This was the best our medical-advanced system had to offer: ‘We’ll save your child’s life now and condemn her to a lifetime of chronic heart issues, secondary cancers, and a host of health uncertainties.’ I felt betrayed.” – Lynn, Parent

“When I completed [cancer] therapy, I was told everything was over and I could go on with my life. What I endured the next 30 years was unexpected, frustrating, physically challenging, and scary, but [it] made me who I am today.” – Greg, Survivor

Patient Perspectives on Treatments

"Why are we only treating the patient once cardiac compromise has already occurred? Cancer survivors, like myself, deserve to live long, fulfilling lives."

- Hannah, Survivor

Meeting Discussion Topic 2: Patient Perspectives on Treatments for Cardiac Late Effects

The afternoon session focused on different approaches for treating and managing cardiac late effects and elicited participants' preferences about potential future treatments. Five panelists – four cancer survivors and one caregiver – provided brief testimonials describing their experiences with treatment for managing cardiac-related medical issues. *Full statements from each panelist can be found in [Appendix 3](#).*



Megan is 38 and was treated for Hodgkin's lymphoma at 14.

At age 32, Megan developed symptoms of a heart attack and had 99% blockage of her left anterior descending artery and needed open heart surgery for a bypass graft. She uses multiple medications for cardiac symptoms. She also uses exercise and dietary changes to manage her disease. She hopes new treatments will be life-thriving and not just lifesaving.



Mariah is 43 and had neuroblastoma treatment at age one.

She tries to exercise and control dietary intake but uses a cane for walking and a wheelchair for longer distances so adequate exercising is difficult. She stated, "I would participate in a clinical trial for a medication that could delay the progression of cardiac late effects. A clinical trial is what ultimately saved my life when I had cancer, so I strongly believe in the importance and promise of them."



Greg had treatment at age 16 for non-Hodgkin's lymphoma.

At age 35, Greg had open heart surgery for valve replacement and bypass. This was followed by a stroke but resolved. He has modified his lifestyle and takes 21 pills a day including for diabetes. In the future, he hopes that we can eliminate cardiovascular toxicities and develop better monitoring systems post treatment.



Hannah is 32 and was treated for osteosarcoma at age 20.

Her cardiac effects were treated with carvedilol, but she experienced hypotension, dizziness, and light-headedness. She then added an ACE inhibitor to her regimen. She stated, "Why are we only treating the patient once cardiac compromise has already occurred? Cancer survivors, like myself, deserve to live long, fulfilling lives."

Marta's daughter Sofia was four when treated for anaplastic large cell non-Hodgkin's lymphoma. Sofia developed heart failure and tried a combination of immunoglobulins and several cardiac drugs, which were effective for 8 years. At age 13 she developed pneumonia and heart failure which led to a blood clot and ECMO treatment, but she developed organ failure and was taken off life support and died.



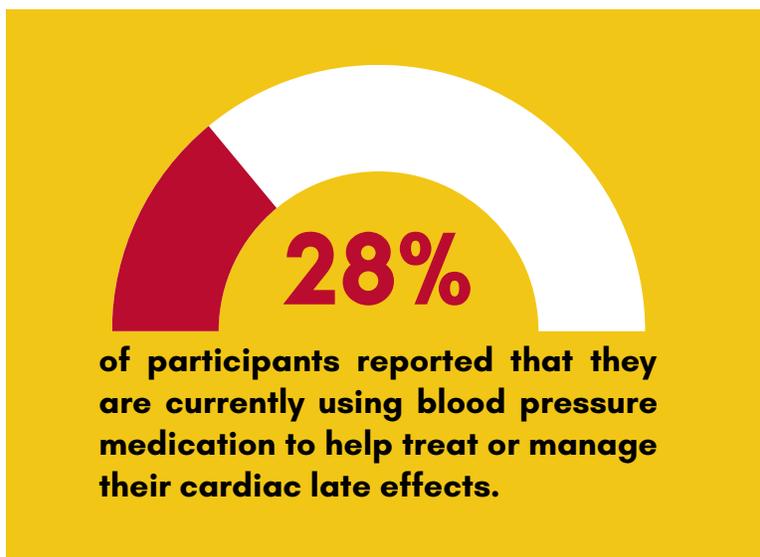
“Ultimately, what we truly need are effective, less toxic childhood cancer treatments that don't include anthracyclines, but until then we must take a team approach to obtain better outcomes.”



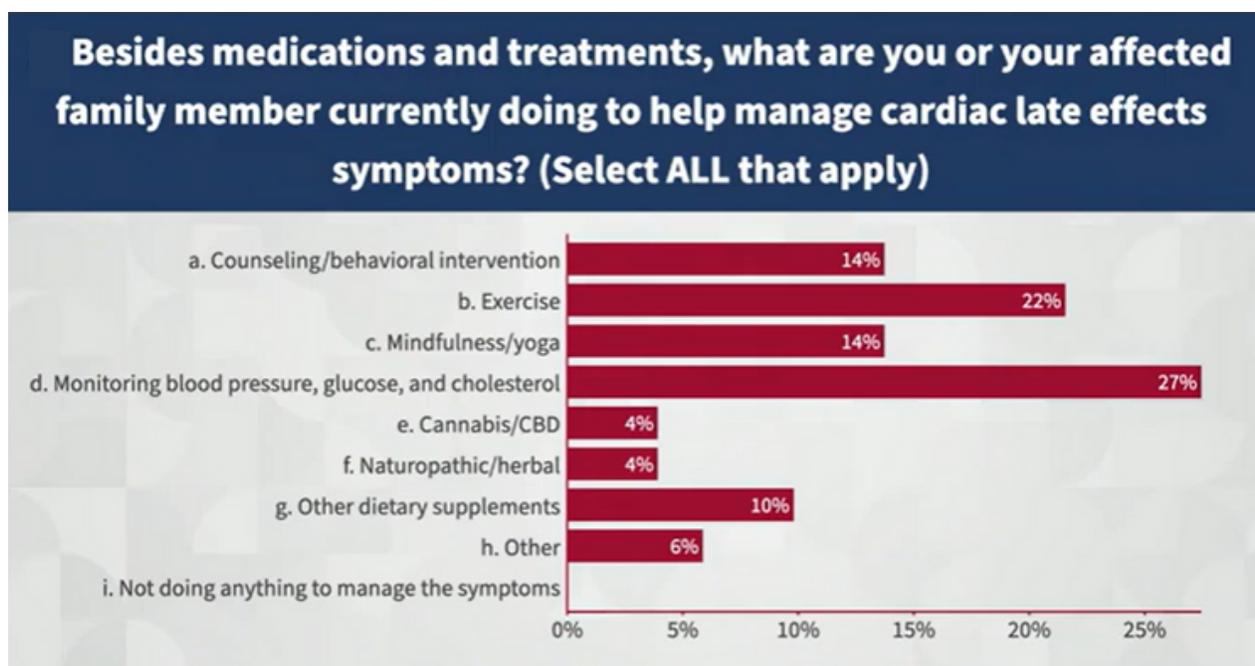
After the panelists spoke, there was commentary by a Zoom panel, followed by meeting participants being led through a moderated discussion with live polling questions and the opportunity to call-in or submit written comments.

Polling: Perspectives on Current Treatments

When asked what medications or treatments they are currently using to treat cardiac late effects, **blood pressure medication** was cited by 28% of participants. Medication for anxiety or depression was cited by 8%, cholesterol medication by 6%, and valve replacement by 4%. Other was cited by 25% and 3% said none.



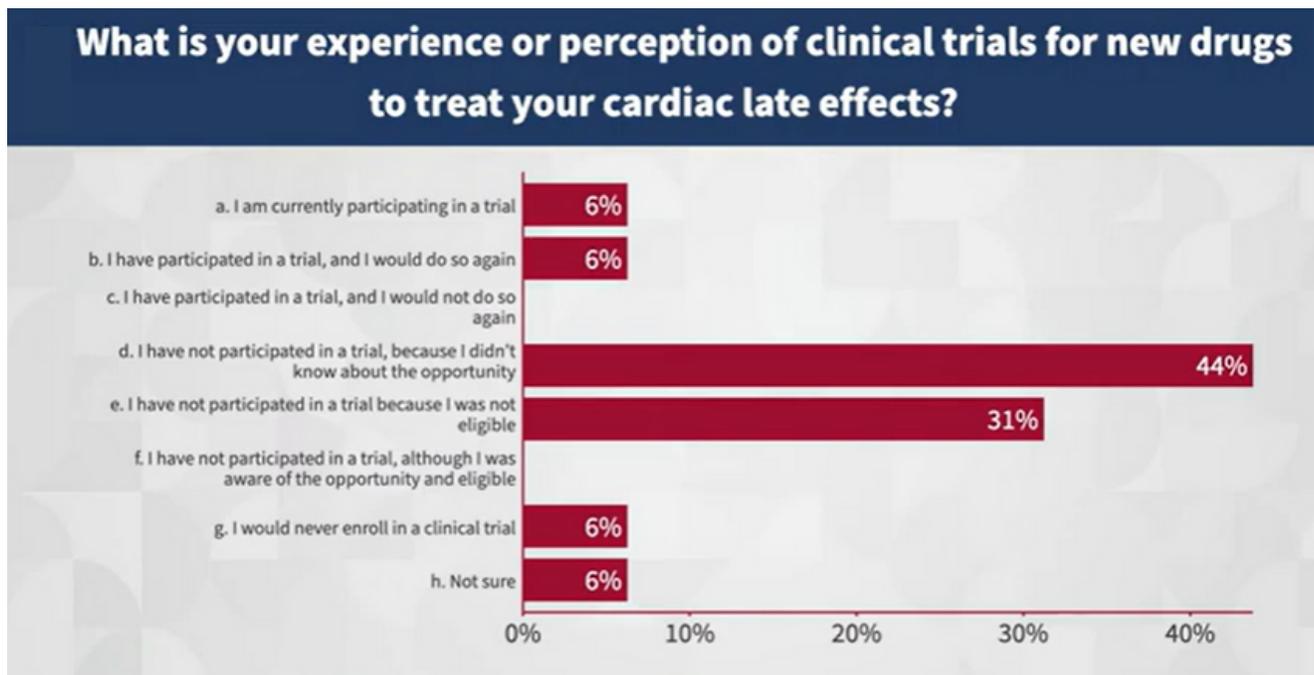
Besides medications and treatments, **monitoring blood pressure, glucose, and cholesterol** was selected by 27% of participants as something they are doing to manage cardiac late effects symptoms. **Exercise** (22%), **counseling/behavioral intervention** (14%), and **mindfulness/yoga** were the next most frequently selected, followed by other dietary supplements (10%), cannabis/CBD (4%), and naturopathic/herbal (4%). Other was selected by 6%.



Polling: Perspectives on Current Treatments, continued

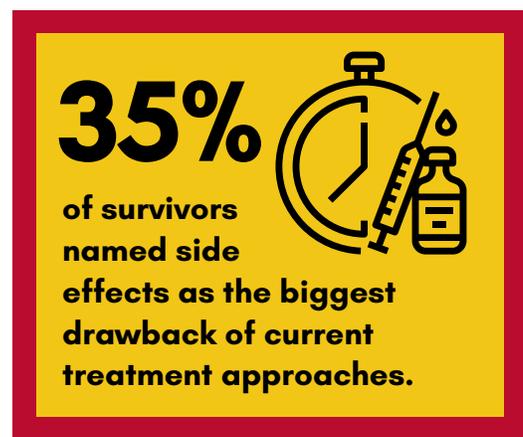
“I think existing clinical trials for cardiac late effects are limited. We need more investment in research that will result in new interventions that can be tested.” -Gregory, Survivor

Regarding clinical trials to evaluate new drugs to treat cardiac late effects, **participants overwhelmingly indicated they have not participated in a trial because [they] didn't know about the opportunity (44%)** and because [they] thought [they] were not eligible (31%).



In assessing how well current medications and other interventions control their cardiac issues, *somewhat* was selected 50% of the time, with 21% selecting *to a great extent* and *not applicable*. No one indicated *very little*, and 7% of responses indicated *not at all*.

When describing the **biggest drawbacks of current approaches, side effects received the most responses (35%)**, followed by *only treats some but not all symptoms/health issues* (15%), *not very effective at treating target symptom/health issue(s)* (13%), *high cost or co-pay, not covered by insurance* (13%), and *other* (13%). *Limited availability or accessibility* received 5% of responses, while *not using any treatment approaches* received 3%.



Medical and Non-Medical Approaches to Address Cardiac Late Effects: Voices of Patients and Caregivers

The following selection of patient and caregiver comments reflects participants' perspectives on the plethora of medical and non-medical approaches they have been using to address cardiac late effects. They provided detailed and poignant commentary about the utility and limitations of various categories of current treatment approaches - including both medical interventions and non-medical efforts such as lifestyle changes - that they are using or have tried in the past, emphasizing the extent to which managing their ongoing health is central to their daily lives.



Medical Interventions

Due to the multiple manifestations of cardiac late effects among pediatric cancer survivors, meeting participants described a diverse and often very large set of drugs and medicines they are using to maintain some balance and stave off more serious heart events. Pediatric cancer survivors rely on a range of medical interventions to manage and mitigate their cardiac late effects, ranging from simple **over-the-counter drugs** like aspirin to routine heart medications for controlling blood pressure, managing cholesterol, and **reducing fluid build-up** in the body. Additional drugs for managing anxiety and depression or related conditions like **diabetes** are also used frequently by these individuals. Survivors often have to adjust their medications to address fluctuations in their vital signs. When standard medications stop being effective, survivors often look to access **experimental approaches** through clinical trials.

"On a daily basis I am reminded of my cardiac limitations, and I've had to modify my lifestyle accordingly. **I take 21 pills a day**, including medication for diabetes and heart failure."
- Greg, Survivor

"[Some of the drugs for cardiac effects] interact with your cancer treatments, and so it just gets tricky. [My daughter] eventually failed all childhood interventions for heart failure and was approved for some adult medication as she then transitioned to [a] cardio-oncology team."
- Patty, Bereaved Parent

"I've been on blood pressure medication since 30. That really was the magical age for me. And making sure that I'm keeping up on my lifestyle habits and doing the right things."
- Angela, Survivor

"Existing clinical trials for cardiac late effects are limited and we need more investment in research that will result in new interventions that can be tested."
- Greg, Survivor

"After my heart surgery, I suffered from systolic congestive heart failure... which required several medications to improve my heart function... Once my dire symptoms improved, we adjusted medications to keep my blood pressure down. Then later to try to lower my tachycardic pulse. To make sure I wasn't retaining fluid, we tried [a series of diuretics]."
- Megan, Survivor

Other Medical Interventions, continued

As cardiac conditions worsen, many pediatric cancer survivors are forced to consider undergoing significant monitoring and must often consider highly invasive surgeries. Meeting participants described their experience with frequent **EKG and echocardiogram exams**, valve replacement procedures, and **heart transplant surgeries**. While these procedures often carry significant risks and require extensive **post-operative rehabilitation**, some meeting participants described their willingness to proceed in hopes of providing some stability to their health and remove some of the fear and uncertainty about the future.



“The decision to go with the surgery seemed like the lesser of the evils. We would have been guessing. We just didn’t have the right medication to try, or we weren’t sure, and so we would have just been trying. And then if it worked, we also didn’t know how long we would have to be on it.” - *Rachel, Parent*

“I have had 48 surgeries, with most related to my cancer or late effects.”
- *Mariah, Survivor*

“[The medication gave [my daughter] more life, and we were hoping, hoping, hoping, for that remodeling and that heart strength, which unfortunately never came. And, so, then the transplant discussion came about with multiple transplant pediatric centers. And, unfortunately, due to chemo side effects and cancer side effects [my daughter] was not eligible. . . and so the LVAD was her only hope and option, yet no children live with LVAD at all for a long period of time. It’s usually a bridge to transplant. But we were hopeful that maybe she could be the one. She pulled off many miracles. Unfortunately, this was not it. And she died of a stroke about a month and a half after LVAD surgery, which she never woke up from.”
- *Patty, Bereaved Parent*

Non-Medical Interventions and Lifestyle Changes

Managing health while dealing with cardiac late effects often includes non-medical approaches and changes to lifestyle. Participants described their focus on **diet and exercise** to exert additional control over their health and minimize future heart incidents. Survivors rely on mindfulness, yoga, and therapy to maintain emotional well-being while pursuing a heart healthy diet and fitness activities to maintain a healthy weight.

"Make sure that your diets are good. Stay off sugar. There's a lot of preventive things. Exercise is so important too, even whatever they can do." - *Linda, Survivor*

"I think we're all shooting for the day where we don't have this type of outcome for survivors. I think about it every day, it affects my life. I can use lifestyle modifications to live a really good life and have a high quality of life, but not everybody has access to the good medical care and expertise, given advice to maximize their outcome, knowing that there's cardiac problems." - *Greg, Survivor*

"I think the medication has helped [my daughter] and particularly now, and the fact that she had to learn to manage this at a very early age. Exercise, I think she's very cognizant of diet and good health. " - *Anna, Parent*

Ongoing Cardiac Monitoring

Survivors and caregivers described the importance of managing through the transition from being a pediatric cancer patient, to survivorship, and then into adult cardiac care. As pediatric cancer survivors move away from their acute cancer treatment and move into adulthood, they need to **find healthcare providers that can provide the appropriate level of ongoing monitoring and care.**

"The most effective things that have helped [my daughter] were good pediatric cardiology care follow up. That changed when she became an adult, and we had a hard time finding adult cardiologists that were really in tune to the needs of these patients." - *Anna, Parent*

"We long survivors need to have teams of specialists to rely on who apply personalized but standard treatments. Survivors often need to beg attention from doctors, oncologists themselves while embarking in new secondary late effects (such as new cancers) and advocate for their rights." - *Elisa, Survivor (Written Comment)*

"YES to getting information to primary care providers!! Many long-term survivors no longer see an oncologist, which puts them further "out of the loop" in being educated on late effects. Far too many primary care physicians have NO idea what to do with us." - *Erin, Survivor (Written Comment)*

Polling: Perspectives on Ideal Treatments for Cardiac Late Effects

When asked to select the most important impacts from a potential new treatment, the top response was **protective treatments to prevent heart effects from cancer treatments** (27%), followed by less toxic cancer treatments with reduced impact on heart health (25%). Improved treatment for symptoms of cardiac late effects and the need to stop further progression of heart disease both received 17% of responses, with the need to recover some heart health receiving 12% and other receiving 2%.

“[P]revention is the biggest goal for us... [i]t would be so amazing if [genetic testing] did become more common practice in our treatment of children so that we can measure those probabilities and then maybe create scans and tests that could predict things.”
- Rachel, Parent

“Prevention is number one. The next one would be to catch changes before they become catastrophic. I think right now there are some medications out there that can do that. They are probably not well-studied in our patient population. That could be part of the problem. [O]pening up the studies to this high-risk population would be huge.” - Linda, Parent

“When I was originally being treated [for pediatric cancer] that protocol was over 40 years old at the time and that was the only protocol that I could be put on. So it’s just very important because our children that are being diagnosed [with cancer] and treated have their whole lives ahead of them and it’s so important that **after everything they’ve been through, their life should be a breeze and it turns out that it’s not.**” - Sarah, Survivor

Developing New Treatments & Management Approaches: **Voices of Survivors and Caregivers**

“We need more options for everyone here and everyone out there dealing with this.” - Patty, Bereaved Parent

As a final set of discussion points for the meeting, participants were asked to further discuss their views on what should be emphasized in the development of new treatments and management approaches for cardiac late effects. Participants urged development of less toxic treatment options for pediatric cancers, while also pressing for better ways to prevent, minimize, and control cardiac late effects.

“There is a desperate need for preventive treatment, as well as treatment and guidelines to address cardiac effects after surviving cancer.” - Hanna, Survivor

“More trials are needed in primary prevention, secondary prevention, and tertiary prevention: [D]esigning treatments or additions to the treatment of primary childhood cancer that greatly reduce the risk of cardiac complications over the life... [Need] more effective screening and [ways] to treat asymptomatic changes found on those screenings... [Look] at how well treatments used in the general population help survivors vs. our population and the specific treatments particular to our population.”
- Jacob, Survivor

“I look at the children [of the future] and say that’s where I want to see a reversal. I want them to be 51 and have fewer problems. I want them to be 51 and have the FDA and whomever have a standard of care and a procedure in place. Or whether it’s an oncologist, another specialist, a general practitioner, there’s something there that talks to their treatments and their long term care... [my] future concern is on the people who will grow up one day, be in our shoes, be in my shoes at this age, and hopefully they’re thriving in ways that maybe I haven’t been able to and they’re having answers a lot sooner.” - Angela, Survivor

Written Comments

During the event and for an additional 30 days after the meeting, participants were invited to submit written comments. A total of 21 written comments were received for inclusion in this report. Many of those comments are included throughout this report, and others are excerpted here. *A full list of comments received is included in [Appendix 3](#).*

➤ “As someone treated so many years ago and now in late-stage heart failure (symptomatically qualified for heart transplant but disqualified due to other late effects), I hope that the FDA will encourage and evaluate the following three questions. 1) Primary prevention—designing treatments or additions to treatment of primary childhood cancer that greatly reduce risk of cardiac complications over the life time; 2) Secondary prevention—both maximizing effectiveness of screening and how or whether to treat asymptomatic changes found on screening (or using cardiac agents like carvedilol in survivors after therapy who are at risk); 3) Tertiary prevention—how well treatments used in general population help survivors vs general population and evaluation of specific treatments particular to us. I also think it would be important to realize that the pathophysiology of radiation and anthracycline cardiac damage are at the very least partially different and that age at treatment —i.e., size of the heart at primary cancer therapy— may affect effectiveness of any of the above approaches.” - *Jacob, Survivor*

➤ “An important aspect of what we are talking about regarding education & early identification is a need for survivors to be seen by capable survivorship clinics. The reality is that we need more survivorship clinics, and more capable clinics to help educate survivors and care providers. We need to make these available to all families, and especially those [whose access] is most challenged: rural families, the economic disadvantaged (more than we think with financial toxicity impacting so many) and some ethnic groups. We can improve the quality of life for so many if we can improve the quality of care for our survivors.” - *Mary Beth, Parent*

"Side effects from cardiotoxicity rob what [survivors] can do, their confidence in themselves and their health, and a reliance in the future."

- *Mary Beth, Parent*

Written Comments, continued

- “One question I would like to ask the FDA would be whether they would agree to include a report like this in their application criteria. For example, on the FDA New Drug Application pages, I’ve copied a section of the page below and suggested an additional bullet point and an additional sentence. Ideally, we want drug manufacturers thinking about long term effects as early as possible. There is also an earlier section on investigational research and maybe something like this could be included there as well. ‘The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions: (Add this question: To what extent can the drug meet the needs expressed in relevant reports from Externally Led Patient Focused Drug Development Meetings? Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks. (Then add this sentence: This includes any risks of adverse long-term effects or secondary diseases that could be caused by the drug’s toxicity.) Whether the drug’s proposed labeling (package insert) is appropriate, and what it should contain. Whether the methods used in manufacturing the drug and the controls used to maintain the drug’s quality are adequate to preserve the drug’s identity, strength, quality, and purity.’ The documentation required in an NDA is supposed to tell the drug’s whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed, and packaged. The following resources provide summaries on NDA content, format, and classification, plus the NDA review process.” – *Simon, Advocate*
- “Cardiac disease, coupled with the reality of complicated health for our survivors, makes for a very huge concern for a life of quality for child/teen. Then add the psychological impact of cardiomyopathy developed, who is watching his grandfather erode away because of cardiac disease. This cannot be overstated. I would imagine it speaks to the need to test prior to chemotherapy to identify those patients who are more genetically prone to cardiac concerns and developing modified treatment to be gentler on the heart while still attacking the tumor. While other side effects have had a more physical impact on my son’s life, the cardiomyopathy – due to extent, family relation, and timing after other progressive issues – has affected my son’s psyche the most. While I’m extremely grateful for today’s survivorship statistics, our children continue to struggle in so many ways as they mature because of these side effects. Side effects resulting from cardiotoxicity rob what they can do, their confidence in themselves and their health, and a reliance in the future.” – *Mary Beth, Parent*

Benefit-Risk Framework

The PFDD process allows patients' voices to inform the development of a benefit-risk framework for use in the evaluation of new treatments. People living with the disease or condition have a unique perspective on the dimensions that are most important and critical to regulatory decision making, the unmet medical needs of others with their condition, and the benefit-risk tradeoffs that may be acceptable across the continuum of the disease.

Incorporating Patient Input Into a Benefit-Risk Framework for Cardiac Late Effects

In 2013, the FDA published a draft implementation plan for a structured approach to benefit-risk assessment in drug regulatory decision making. Updated in 2018, this plan currently reflects a requirement of the 21st Century Cures Act that the agency issue guidance on how patient experience data will be incorporated into the structured benefit-risk assessment framework to inform regulatory decision making.

The structured benefit-risk assessment framework calls for assessment of four decision factors:



When completed for a specific product, this framework summarizes each decision factor and explains the FDA’s rationale for its regulatory decision. The benefit-risk framework is important for both regulatory and treatment decisions.

The PFDD process allows patients’ voices to inform the development of a benefit-risk framework for use in the evaluation of new treatments. People living with the disease or condition have a unique perspective on the dimensions that are most important and critical to regulatory decision making, the unmet medical needs of others with their condition, and the benefit-risk tradeoffs that may be acceptable across the continuum of the disease. Their input thus should **guide therapeutic development** to ensure that treatments have clinical meaningfulness and address aspects of disease that are most critical to people living with the disease.

Information generated during the EL-PFDD on cardiac late effects provides important insights for therapy developers and regulators seeking to reflect the perspective of people with cardiac late effects. Armed with these insights, drug developers should be better able to design clinical trials to assess outcomes that are clinically meaningful and, hopefully, achieve a higher chance of success. Likewise, defining benefit expectations and risk tolerance among people with cardiac late effects when considering various treatment options should enable **better characterization of tradeoff decisions** faced by patients, families, and healthcare providers, as well as regulators.

Input provided by people impacted by cardiac late effects during the EL-PFDD is summarized here in this sample framework (Table 1) to provide all stakeholders with an understanding of the potential benefit-risk aspects for these decision factors. This sample framework is likely to evolve over time and could be incorporated into a benefit-risk assessment framework for a specific cardiac late effect therapy under review in the future.

TABLE 1. SAMPLE BENEFIT-RISK DIMENSIONS FOR CARDIAC LATE EFFECTS

	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
ANALYSIS OF CONDITION	<ul style="list-style-type: none"> • Treatments used to treat pediatric cancers were developed decades ago. • While anthracyclines are often successful in extending survival, they also often lead to cardiac late effects. • Additional risks of cardiac late effects include receiving chest radiation, young age (for cancer treatment), being female, & other cardiovascular risk factors. • There is higher risk for non-white pediatric cancer survivors due to higher risk of cardiovascular conditions. 	<ul style="list-style-type: none"> • There is a high unmet need for pediatric cancer survivors who suffer cardiac late effects from their cancer treatments. • There are few effective medical interventions to prevent or successfully treat cardiac late effects of pediatric cancer treatments. • Research is needed to develop pediatric cancer therapy that moves away from anthracyclines and is less toxic.
IMPACT ON ACTIVITIES OF DAILY LIVING	<ul style="list-style-type: none"> • Pediatric cancer survivors and their families face significant physical, emotional, quality of life, and logistical burdens due to their late effect heart conditions. • Cardiac late effects impact individuals' ability to work, conduct basic life tasks, exercise, engage socially and pursue family goals. • Anxiety and fear are major aspects of living with cardiac late effects. 	<ul style="list-style-type: none"> • Additional effective approaches for preventing and managing cardiac late effects are needed.
CURRENT TREATMENT OPTIONS	<ul style="list-style-type: none"> • Drugs, devices, and procedures are all employed frequently (and often in parallel or sequentially) by individuals with cardiac late effects. • Non-medical treatment options and lifestyle changes are also used routinely. • There are no good options to prevent cardiac late effects from occurring or to effectively intervene before they progress/become serious. 	<ul style="list-style-type: none"> • There are many gaps and areas within the array of cardiac late effects that currently lack effective treatments. • Specialized follow up for pediatric cancer survivors is needed. • Families and survivors should have an understanding of their risks and what to watch out for.
FUTURE TREATMENT OPTIONS	<p>Patients and caregivers seek:</p> <ul style="list-style-type: none"> • Less toxic pediatric cancer treatments • Treatments to prevent cardiac late effects • Ways to identify genetic factors that increase individuals' future risk • Effective interventions to mitigate cardiac late effects before they become serious • Opportunities to learn about and participate in clinical trials, as appropriate 	<p>Additional research and development are needed to develop:</p> <ul style="list-style-type: none"> • Less toxic pediatric cancer treatments • Cardio-preventive measures • Approaches to stop progression of late effects • Models to identify individuals and sub-populations that may be at higher risk so that treatment can be adjusted accordingly

Conclusion & Acknowledgements

Survivors and families who are dealing with cardiac late effects have often felt alone and confused by the condition. There continues to be a tremendous unmet medical need for people living with cardiac late effects. This public forum summarizes the experiences and needs of the survivor and caregiver community and will help provide vital input to regulators, clinicians, and product developers who share an interest in improving treatment approaches.

Children's Cancer Cause is proud to have led the effort to host this meeting, and we remain grateful to the many individuals who stepped forward to share their stories, described the impact that cardiac late effects have had on their lives, and shared their fears and hopes for the future.

Our deepest thanks to advisors, sponsors and participants who helped in the successful execution of this EL-PFDD.



"The impact of this meeting & your collective voice will be felt for years to come."

*- Steve Wosahla, CEO
Children's Cancer Cause*

Appendices

- Appendix 1: [Meeting Agenda & Discussion Questions](#)
- Appendix 2: [Survivor and Caregiver Panel Participants](#)
- Appendix 3: [Panelist Statements & Submitted Written Comments](#)
- Appendix 4: [Meeting Polling Questions & Responses](#)
- Appendix 5: [Link to Meeting Recording](#)

This report is in memory of Abby (pictured right), Sofia, and every child who has died from the cardiac late effects of their cancer treatment.



**"Hopefully [future survivors] are thriving
in ways that maybe I haven't been able to
and they're having answers a lot sooner."**

- Angela, Survivor

