

Appendix 3: Panelist Statements and Written Comments

Panelist Statements

Panel 1

Kelsey: Hello my name is Kelsey, I am 29 years old and I live in Carlsbad, California. I was diagnosed with Juvenile Mylo-Monocytic Leukemia (JMML) at the age of 3. I had full body radiation, chemotherapy as well as a bone marrow transplant which I relapsed shortly after from. The Graft versus Host Disease effect or GVHD and what little of the “good Kristy cells”, as my mom would say, I had left in my body is what helped put me back into remission; Kristy being my bone marrow donor and my hero to this very day.

Today, 25 years in remission and months shy of my 30th birthday (hard to believe); I have started to notice the delayed effects of cardiac issues are becoming more and more apparent to me now that I am older. The two main cardiac issues that are having most significant impact on my life so far would be; the high blood pressure and tachycardia.

I first started to notice the high blood pressure in college around 2013 and my mom thought it was related to stress, granted she was probably right since I was up to my neck with school-work and juggling a job at the time. The doctor put me on medication and it helped for the meantime to lower my crazy 150ish blood pressure to a normal level. After about two years on that medication my blood pressure leveled back out and I got off of it and also starting a new school helped a lot. But then I started having new issues with palpitations and chest pains. The chest pains and palpitations kind of felt like a dull and achy pain, but they come out of nowhere so I don't really know when to expect them which, is really frustrating. One of my first episodes with the chest pain was back in 2015 at work and I was just standing there doing nothing and all of a sudden had a stabbing pain in my chest. That night it urged me to seek help because it was nothing like I had ever felt before. I know heart attack symptoms are a lot different in women so, yes that definitely scared me. The doctor unfortunately could not figure out why I was having chest pain or palpitations, so that issue went unsolved.

Then a year later, I started having issues with tachycardia around 2017. I feel like the tachycardia effects me the most because I don't know when it's going to happen and it can happen at any moment as well as at any time of the day. Before I was put on the medication, the tachycardia seemed like it interfered with every part of my life; simple tasks at work like just walking up the stairs to the break room or standing still doing nothing, it really came out of nowhere and my heart would be racing. The tachycardia still impacts my life today even though I am on medication, things such as; exercising or playing sports, hanging out with family or doing stuff outdoors like hiking. I can normally feel it when it starts to spike, my chest will start

pounding and it literally feels like my heart is beating out of my chest, definitely not a great feeling. It doesn't really hurt but, it's just a very uncomfortable feeling. I've never told any of my friends about the tachycardia because it has not come up plus I am kind of private person, only my closest friends know about my cancer history. I have told some of my family members about the tachycardia because I recently found out that some of my family members have the condition as well and that it is hereditary. My doctor thought the tachycardia might have been stress-related or possibly situational tachycardia but could never really figure out why it was happening. I do have to get yearly echocardiograms to make sure my heart is healthy and functioning properly so, that does help. I am no longer on medication for my high blood pressure but the one I am taking for tachycardia, Metoprolol, actually is supposed to help with high blood pressure so, it is being maintained somewhat at the moment. However, I do have migraines as well so when I have a bad migraine attack or any other severe pain it gets really high, which I do have to watch closely. As of right now, I am not experiencing any acute problems but, in years past it's been disappoint after disappoint after getting told we don't what's wrong and 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.

Lynn: Daily I look at my child and question is today the day? It's a thought that fights its way to the center of my heart no matter how hard I try to keep it buried. I am constantly looking for the signs.... is she out of breath, does she look worried, is she nauseous, does she have stomach pain? I know this annoys her and I try not to be obnoxious about it - but this is my everyday reality.

My name is Lynn and I am Mom to my daughter Peyton. who was diagnosed in 2015 with embryonal liver sarcoma. Given a 30 percent chance of surviving her cancer she was treated with several surgeries, 6 rounds of doxorubicin and Oxoamide and 6 weeks of radiation. I remember asking her doctor at our first visit what are her treatment options. The doctor replied tenderly and simply "there's only one." She proceeded to explain the cocktail that would potentially save my daughter's life and how it would be administered. She then explained the immediate side effects and slipped in that there would be long term side effects, but we would worry about them after the initial phase of treatment. My head was swimming.

That night I woke up at 3 am panicked. Long term side effects? 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 advanced medical 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 host of other health uncertainties. I felt betrayed. Two days later she was admitted and received her first treatment. As the nurse pushed the syringe to administer "the red devil concoction" I took a deep breath and smiled as I held my daughter's

hand. I had no choice -this was the only option availablethis is what had to be done -come what may. It was at that moment that the mental consequences of cardiac late effects began haunting my thoughts, hopes and dreams for my precious child.

Peyton is now 17, a smart, conscientious and beautiful young lady. We have fought hard to get her here. She is considered a cancer survivor. We have her yearly 504 review in school and every meeting they push to remove her accommodations stating accusingly, "she looks perfectly healthy." And I reply that tomorrow she may not be...let's leave them in place -- they have no idea of the late effect ticking time bomb inside her..." Peyton goes yearly to see a plethora of doctors including her cardiologist to check on her heart health- it's just what we do. She takes a day off of school for each visit, we leave early in the morning, spend hours at the doctor's office as they run tests. I hold my breath every time we go waiting for the results that will confirm she has more time until her heart shows signs of late effects. I know the clock is ticking- and I live in fear of when that day arrives.

Peyton goes to great lengths to hide her cancer diagnosis. She wants everyone to think she is a completely 'invincible teenage - normal.' And she tries to be -- but she harbors intense anxiety about her body. Not the typical teenage stuff like does my hair look ok- deep hidden and isolating fear. Entering high school she was looking forward to joining the cross country team- She enjoyed running and would often just go off on a jog on her own. The day after her a routine cardiology appointment- I picked her up after her first practice and she was inconsolable. She had felt the hard beating of her heart as she ran and it sent her into a panic. Her thoughts were intricately compounded. Not only was she fearful of physical pounding of her heart and the looming indication of chronic heart issues, but also the psychological realization that her teammates might learn of her cancer and think of her as "not normal." The thought was too intense for her to overcome. She quit the team the next day.

It breaks my heart to know that the only means of saving her life condemned her to a lifetime of debilitating chronic-physical and mental issues. If only there had been a therapy that would have minimized or eliminated the cardiac late effects -my baby's life would be so different. I live with the fear of "will this be the day and how will we manage the late effects phase of my child's cancer." Cancer is a restless and relentless disease that affects the mental and physical health of my daughter and our family for a lifetime. I implore the FDA.... seek out new treatments that are both preventive and curative to eliminate cardiac late effects on our pediatric cancer survivors.

Susan: My name is Susan, and I live in Colorado. Bette Davis once said, "aging is not for sissies." Aging as a survivor of childhood cancer is terrifying. Ten years ago, at a routine appointment, my PCP said, "Your heart murmur is changing. Let's send you to a cardiologist." An echocardiogram revealed severe aortic stenosis. The cardiologist said I would need heart valve

replacement. He explained that the stenosis was caused by the 36 grey high-dose mantle radiation I had received in 1983— when at 17, I was diagnosed with Hodgkin lymphoma.

I was shocked. Cancer as a teenager had become a distant memory...The staging laparotomy and splenectomy, lymphangiogram, bone marrow biopsy, MOPP chemotherapy, radiation...the impact of that brutal year seemed distant and unreal. At age 22, I had reached the 5-year survival mark. I was released from cancer care and told to go live my life. No one suggested the need for any special follow-up.

Shortly after radiation treatment, I was diagnosed with hypothyroidism. I learned to live with that-- along with secondary infertility, premature menopause, and constant neck and upper back pain from radiation fibrosis. In 2014, just after my 49th birthday, I had aortic valve replacement.

I realized I had spent my life thinking I would be lucky to live to be 50. While in the hospital for my valve, I met a cardio-oncologist who saw patients in the oncology clinic. I didn't expect the strong physical and emotional reaction I would experience when entering a cancer clinic after 30 years. By the time the nurse came into the exam room, I was nauseous, shaking, and teary. I apologized and told the nurse "I don't know why I'm suddenly falling apart!" She kindly said it was common for cancer survivors to respond this way.

Only two years after my heart valve replacement, I received my first-ever call-back after a mammogram. The radiologist told me the calcifications were likely benign and recommended that I follow-up in 6 months. My PCP wanted to be proactive, so instead of waiting, I scheduled a biopsy. Two weeks later, I received the pathology report: Cancer. Again.

Nine weeks after this new diagnosis, I took a leave-of-absence from full-time teaching and underwent a double mastectomy. I was treated with 12 weeks of chemo and 12 months of Herceptin, which carries a risk of heart failure. After experiencing valve disease and breast cancer as direct results from radiation treatment, the risk of heart failure felt all too real.

I told my doctor, "I know that late effects are here. What I don't know is whether I'm standing at the edge of a glacier or in the direct path of an avalanche." In 2019, I applied for disability retirement from teaching. To look at me, no one would ever guess I have serious health issues. My breast oncologist once said, "Susan, you're in pretty good shape for the shape that you're in!"

Traveling more than an hour each way to see various specialists has become a way of life. I see a cardiac electrophysiologist, interventional cardiologist, and cardio-oncologist. I see a gastroenterologist for esophageal issues. And an ENT for partial paralysis of my left vocal cord. 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. I also see a trauma psychologist who uses EMDR to treat the PTSD symptoms that began with childhood cancer. When treatment ends, cancer is not won OR done. The effects of childhood cancer last a lifetime, and survival comes at a great cost.

Charlene: We are Charlene and Dan, parents to our daughter Ruth who was diagnosed with stage 4 Neuroblastoma at age 5, this year she will be a 16 year survivor. Her treatment was everything we could do for neuroblastoma at the time for slim survival rates that are about 33%. Children with stage 4 neuroblastoma used to be admitted to the hospital and made comfortable until they passed. Now children survive but with the damage we inflict during treatment that a child has to live with for the rest of their lives. Lifelong effects that Ruth has is decreased heart function due to damage done to her heart from the doxorubicin and chest radiation, decreased lung function from chemo and radiation to her chest, hypothyroidism, Horner's syndrome on her left side from the removal of the tumor on the nerve that controls sweat and her left eye lid, ovarian failure from high dose chemo, decreased tooth roots from chemo and radiation, low growth hormone, osteoporosis, bone and joint pain, neuropathy on left arm, food allergies, sensitive skin, and scoliosis induced by her chest tumor resection. Her scoliosis is left to right and front to back. It has been determined that her spine and chest are leaning on the left side of heart and lungs and it is looking like two major chest and spine surgeries will need to be done to bring relief to her heart and lungs. After her first meeting with her adult cardiologist to access her heart rate and function it was determined that her heart function was decreasing slightly

With high dose chemo, radiation to primary tumor areas in her left chest that included her lung and heart, immediately caused her lung function to be about 50% and to have cardiomyopathy. For over ten years her heart function was below normal but stable enough not needing heart medicine to decrease her high heart rate. About 5 years ago we notice a decrease in lung function and increased heart rate. Slowly her chest decreasing in size actually crushing her left side of her heart and not leaving enough room for her lungs to expand to her 50% capacity she lived with for over 10 years. Ruth is currently on metoprolol and a portable oxygen concentrator at age 21 this year. This is the lifelong side effect that hampers every part of her life and is causing her to look in to the possibility of multiple surgeries to physically expand her chest.

Currently, Ruth has mobility issues with any walking or standing for periods of more than a couple of minutes. When traveling she has to utilize a wheelchair. With these limits, Ruth has been unable to experience obtaining her first job or go off to college on her own. When COVID lockdowns were implemented, the bombardment of fear being reported was a constant reminder of how fragile her health is and increased anxiety and feelings of depression. In 2021 she was hospitalized for 6 days because her left lung collapsed. She recovered from the collapse

but is still trying to recover her weight she lost. Eating has been an issue which cause her weight to be low.

Her social life is affected. She is not able to keep up with her friends. Her friends are living at college or working or socializing, she is invited but is not able many times to accept invitations as she is not able to walk as far as her friends. Ruth loves to be in the ocean and canoe sailing in the past. She has been a part of a canoe sailing program for 10 years, current heart and lung situation has caused her not to be able to sail like she did before. When you are in the ocean the water presses against you and she is no longer feeling comfortable to sail, her current health has taken her confidence of being safe in the water. She also does not want to be a burden to her friends.

Ruth is an avid baker and cook and if she is in the kitchen she uses a stool as she gets tired standing and needs to rest when walking.

Ruth has had a couple of little side businesses that she did but her days that she does not feel strong enough are more and more, so her small business have been put on hold.

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.

Ruth is always included in talks and decisions as age appropriate and we asked her doctors, and nurses to speak to Ruth directly during appointments.. We wanted to include Ruth in discussions we always had the glimmer of hope.

A bomb is still a bomb no matter what type of bomb shelter you are in. Don't get dead because once that happens, everything else is toast.

It is a constant balancing act to live with decreased heart function and transitioning to adult care. Parents always hold a very heavy burden on whether they made the best decision on treatment especially when serious lifelong effects are being experiences like heart issues.

Patty: Hello I am Patty and I live in Virginia Beach, Virginia. I would like to introduce you to my beautiful daughter Abby who is forever 15. Abby was initially diagnosed in 2011, age 4, with Philadelphia chromosome positive ALL (leukemia) and given a 20% chance of survival. Abby began a trial treatment, along with chemotherapy for an intense 18 months. Included in her regimen were numerous doses of doxorubicin which we were warned of cardiotoxicity. But at that point, saving our daughter's life was our only choice. Abby fought hard for 3 years with many bumps in the road and ultimately prevailed cancer free. Unfortunately, Abby's cancer returned in 2014 just one week into her 3rd grade year. While preparing for a bone marrow transplant a cardiologist found that she was in heart failure, even though she had no symptoms.

The cardiologist explained that she had cardiomyopathy, caused by the previous chemo treatments.

The treatments that saved her life were now compromising her life. Not only did we have a child battling cancer for a second time, but she had heart failure, AND, her bone marrow transplant was on hold due to this major roadblock.

It was a whirlwind of learning a whole new world of cardiac intensive care. We were warned that her heart medication would be life long, and she potentially would need a heart transplant in 5-7 years but they were unsure as this drug was so new. We heard those words, not realizing that it would ultimately be what took our sweet girl's life.

Abby's care required frequent trips to many doctors 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. Abby had no quality of life and needed home nursing care for years.

Abby slept propped up on at least 3 pillows. because laying flat made her feel as if she couldn't breathe. This made needed CT and MRIs difficult. Abby was homebound schooled 3rd, 4th, 5th and also 6-9th grade, with a few months of being AT school for a few hours at a time. As Abby's friends' independence grew as pre-teens and teens, Abby became more dependent. Abby frequently was exhausted and slept often. Daily she had intestinal difficulties, nausea, vomiting and diarrhea. She had a G-tube to help regulate her fluid intake. Abby was in pain much of the time which was managed with long term methadone, frequently requiring stronger pain medication or IV interventions. Her kidneys were hit hard, and she became a diabetic dependent on immense amounts of insulin. Abby couldn't eat what she wanted as her body didn't process things the same. Infections continued. She slowly lost mobility. Outside of the house Abby was in a wheelchair and graduated to an electric wheelchair. Closer to the end we often carried her within the house and had a stair lift.

Being with friends she could just sit and chat or play a game. Sleepovers and being at friends' houses soon came out of the question. Even with her few activities we had to make sure there was someone with nursing experience present or I stayed nearby.

Abby had dreams of being a chef and owning her own restaurant. She even received a full scholarship to the Culinary Institute of Virginia. Abby couldn't stand for long periods of time, so we'd set up a place to sit, chop and stir but this made other parts more difficult. Try making dinner from a chair.

IV medications helped for a while but soon our cardio oncologist discussed the need for a heart transplant. As we talked with transplant experts it became apparent that Abby would not be a candidate for a heart transplant. Her only option was a Left Ventricular Assis Device and there are no other kids that live long term with an LVAD. Hopeful that was going to give her time on

this earth with some quality of life, Abby entered surgery on September 7, 2021, and never woke up. Post-surgery, she suffered a stroke and passed away October 19, forever 15.

I am here because my daughter's life ended due to cardiac long term effects and she ran out of treatment options. Please keep working to find more drugs that can help. Abby's tremendous fight and inspiring drive to live through it all lives on in me. My greatest hope with my work and sharing her story is that other families and children do not have to go through what Abby did for 11 of her 15 years on this earth. Thank you.

Panel 2

Greg: Hi, my name is Greg. I am an Associate Professor of Pediatrics and Physician Scientist at Greehey Children's Cancer Research Institute in San Antonio, TX. My professional efforts and career are focused on improving the quality of life for the growing population of childhood cancer survivors and to use laboratory investigation to better understand how our successful treatment regimens damage the cardiovascular system. But I am not speaking on this subject today as a physician or a lab researcher. I am here today as a patient.

In 1989 at the age of 16 I was diagnosed with Hodgkin's disease. This was a major life-changing event for me and one that changed my life trajectory in so many significant ways, some bad and some good. Looking back over the past 30 plus years as a survivor, I can tell you I have been tremendously blessed by my experiences as a cancer patient and survivor and that the benefits of these experiences has far outweighed the obstacles and daily struggles.

I was treated in an era when higher doses of anthracycline chemotherapies and extensive radiation were used to successfully cure Hodgkin's disease in over 90% of patients. Going through the year and a half of these treatments was physically and mentally challenging. When I completed the 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.

My life as a pediatric cancer survivor has closely paralleled many of the key findings that have been published over the years that have detailed the extensive health complications survivors face and many of these have been cardiovascular. As I pursued my MD/PhD degrees, pediatrics residency, hematology-oncology fellowship, established an early academic career, and my wife and I raised two sets of twins, I have also had to overcome numerous health obstacles. These have been a constant reminder that our work as pediatric oncologists and researchers is not even close to a point where we can declare victory of childhood cancer.

At age 35 during my first year of pediatric hematology-oncology fellowship I underwent open-heart surgery to replace a badly damaged aortic valve and to bypass 3 coronary arteries that were 95% blocked. A few years later, I had a stroke and was unable to move the left side of my body for about 35 minutes – fortunately my symptoms resolved without intervention, and I was

left with no permanent damage. I continue with close care by cardiology, as I have subsequently developed congestive heart failure requiring close medical management and an additional heart valve that at some point will also need to be replaced. To me, cardiovascular complications of successful childhood cancer therapy are all too real.

On a daily basis, I am reminded of my cardiac limitations and I have had to modify my lifestyle accordingly. I take 21 pills a day, including medications for diabetes and heart failure. I limit my exercise to walking and avoid walking up stairs or hills. I limit yard work and other strenuous activities. The activities I participate in with my family are often affected by my limitations. All of this can be frustrating, but when I begin to feel sorry about my situation, I remind myself of the many kids and families I have known over the last 30 years that suffered a far worse outcome.

I wanted to end my time by highlighting the hope I have for future pediatric oncology patients. We have made progress in lessening cardiovascular complications through strategies such as decreasing drug doses and better targeting radiation. More importantly, I believe we have the scientific and clinical expertise to completely avoid this outcome. But we must make eliminating cardiovascular toxicity a central goal of oncology efforts in the coming decades. We need to develop new ways of protecting the heart during exposure to cardiotoxic treatments, more selectively deliver drugs to tumors, and develop the clinical infrastructure to closely monitor the health of all survivors. I would consider anything less a failure. I strongly believe that a day when pediatric cancer patients can survive with normal cardiac health is within reach.

Marta: My name is Marta and I welcome the opportunity to share my daughter's story. In December 2003 Sofia was 4 when she was hospitalized after several days of a painful, enlarged lymph node in her left groin, constant fever, fatigue, etc. and two antibiotics. That night in the ICU I saw Sofia's WBC count and asked an intern if they thought it was cancer. Her response was that sometimes knowing a little was worse than knowing anything at all.

As it turned out Sofia did have cancer, but we needed to biopsy the lymph node to determine the exact type BUT frankly our biggest concern at the time was that Sofia was struggling to breathe and the physicians couldn't figure out why, saying it was a separate issue to her cancer. When Sofia came out of the surgery she was on a respirator and in less than 24 hours she was maxing and needed an oscillator, so she was transported to Miami Children's. In less than 24 hours Sofia was on ECMO with initial biopsy results inconclusive. Eventually Sofia was diagnosed with Anaplastic Large Cell Non-Hodgkin's Lymphoma with small cell variant and while on ECMO was started on POG9315. Sofia responded very well to treatment and within a few days her lungs began to clear. She left the hospital after 5 weeks and while still in shock we felt the worst was over.

However, that August Sofia couldn't sleep but wasn't able to verbalize exactly what she felt. Sofia didn't look well and because of her initial presentation I knew her breathing wasn't right. She was seen by one of the oncologists who said because of the fever they'd have to admit her, but she wasn't worried. BUT I WAS! Doctors didn't hear anything in her chest but I told them to please go check the chest x-ray which had just been taken. By now it was shift change and a young nurse came in to do vitals but couldn't get a pulse. She ran out of the room to get help. Finally, someone was listening to me!

Sofia was taken to the pediatric intensive care unit where we were told she was in heart failure. Sofia was stabilized without major intervention so we, along with the PICU docs, oncologists and cardiologists thought it was viral. She was transferred to the Cardiac ICU for better monitoring and there we were welcomed by the head of the unit with these words said in front of Sofia: Think you should know that Sofia will need a heart transplant, but she won't get it because she's in treatment for lymphoma so there's not much we can do.

After this experience, we sought the advice of a cardiologist at the University of Miami who then sent a letter to the Cardiologists at Children's with a recommended course of treatment new to children but which we were more than willing to follow. This included infused Immunoglobulin, a heart biopsy, Enalapril, an ACE-inhibitor, Coreg, a beta-blocker and a diuretic. Sofia's cardiology care was now in the hands of the cardiologists at University of Miami.

In December 2004 Sofia finished her treatment and within a couple of years was weaned of all cardio meds except for the enalapril. For almost 8 years Sofia lived a fairly normal life but ultimately we learned the damage to her heart wasn't from a virus but from the anthracycline Adriamycin given as part of her cancer treatment and in the summer of 2011 Sofia's function started to go down. She was put back on the Coreg and in December a diuretic. In March 2012 after her 13th birthday Sofia got a cold which turned into walking pneumonia and another heart failure diagnosis.

Sofia was hospitalized and within 24 hours had a stroke which the doctor initially said was a syncope as she'd just eaten. I actually had to follow him out of the room to get him to take me seriously as I knew it was a stroke.

When they started the ECHO-cardiogram the first thing I said to him as I pointed to the monitor is, "Isn't that a clot?"

Sofia seemed stable but a few of days later crashed and was put on ECMO again but because of scarring they had to go through her chest. Docs did all they could for a heart transplant even putting a Left Ventricular Assist Device (LVAD) and then a Right Ventricular Assist Device (RVAD). However, Sofia's organs started to fail and then got a fungal infection. On Tuesday, April 3, 2012, we made the decision to disconnect our 13 year old daughter and say goodbye.

I learned to advocate for Sofia at every turn and continue doing so today. I think it's important for oncologists and cardiologists to be better prepared to see and treat other Sofia's. They need to know how to diagnose them properly, early and provide the best treatment possible.

Ultimately, what we truly need are effective, less toxic childhood cancer treatments that don't include anthracyclines. And if a cardio-protective agent been available in 2003 Sofia could be alive today with or without less severe cardiac issues. Either way she would've had a better chance for a longer, more impactful life.

Megan: Howdy, my name's Megan. I'm 38 years old and I live north of Houston, Texas, with my husband and 2 cats. I was diagnosed with Hodgkin's Disease Lymphoma just after turning 14, and underwent chemotherapy, radiation, and an autologous bone marrow transplant. During which I started high school bald, so - a huge blow to my social life.

At 32, I developed symptoms of a heart attack (you know, women's symptoms DIFFER from men's!), and was found to have a 99% blockage of my Left Anterior Descending Artery. The cardiologist doing the angiogram cried out, "This can't be real!" and left the procedure room without telling me anything. He told my family that they only found this sort of thing on dead patients. I needed a full open-heart bypass and graft for the artery, which my surgeon theorized was caused by radiation treatment to the mantle (32 Grays' worth) – though could also have been worsened by the doxorubicin.

Before that point, I was taking a low-dose aspirin, niacin, and fish oil as recommended by my GP, as well as a cholesterol-lowering medication. My long-term team kept tabs on my heart with an annual EKG and Echo scan, and I always tested just under a normal Ejection Fraction Rate, at about 55-60 percent. They pushed losing weight, regular exercise, and healthy food options as the best prevention of further problems. The same thing you hear from every doctor, but it's different for cancer survivors.

After my heart surgery, I suffered from systolic Congestive Heart Failure with my Ejection Fraction Rate down to 30-35 percent, which required several medications to improve my heart function: Cozaar (generic losartan), Toprol (generic metoprolol), and Aldactone (generic spironolactone). 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 hydrochlorothiazide but it wasn't strong enough, so we moved to Lasix (generic furosemide).

About a year after my heart surgery, I realized that 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, getting treatment for my Major Depressive Disorder and unrealized long-term General Anxiety Disorder, and I started talk

therapy. My mental health has become as important as my physical health to me. They are unavoidably linked. With my therapist, I work on releasing my stress, meditation, mindfulness, deep breathing, and practicing gratitude: these help to reduce the strain on my heart and pull my pulse down.

Speaking of stress, I can't hold a part-time job, let alone a full-time one. I (somewhat-jokingly) tell people that my health is my full-time job. Because it really is. When you take pills 7 times a day and see doctors up to 5 times a week, it gets to be all-consuming. I check my blood pressure and pulse three times a day. I make sure that I have a bathroom available for about 4 hours after taking my fluid pill in the morning because I'll need to go at least every hour. I break the house cleaning schedule into a little bit every day to try to keep it clean - I physically CAN'T do it all at once. My parents and I swap notes on meds and surgeries, because they are going through a lot of what I am, as they climb towards 70. I feel like I'm older than they are. They probably worry about out-living me.

Recently, I was having concerning symptoms that I thought it wise to see the cardiologist again. My EKG and Echo were "as expected," but my nuclear stress test came back abnormal. An angiogram found that one of the 2 grafts I had 5 years ago had occluded. So, now we're treating symptoms with Ranolazine, along with working to lose weight, increase exercise, and eat healthier.

Even though there are precautions put into place for cancer treatment, they're not enough to keep from long-term effects harming the patient. Even though my radiation treatment had a thyroid guard, I developed nodules and had half of my thyroid removed. Treatments for cancer were not precise enough to kill off the bad cells and leave my good ones alone. I believe that medical nanobots or some other pinpoint treatment would be the best approach to eliminating the cancer cells, especially in the case of blood cancers. Or possibly some sort of hemodialysis where cancer cells are filtered out. Of course, there are always hazards in any medical treatment or procedure, so the benefits would need to outweigh the risks. I hope these types of solutions will be life-thriving and not just lifesaving.

Hannah: Hi all, my name is Hannah. I am a 32-year-old osteosarcoma survivor from Southern California. I was diagnosed when I was 20 years old. Hearing that you have cancer when your life is supposed to just be starting really threw a wrench into all that I had "planned." I had dreams and aspirations of becoming a physical therapist, I was living out of state and finding my own independence and personal identity. Little did I know my world was going to drastically change forever. I managed to make it through my diagnosis, 11 months of chemotherapy, and a few major surgeries to remove my tumor and reconstruct my right leg. When I completed treatment in June of 2011, I was naïve and thought "Well, that's done. It's time to move on and make something of my life."

Fast forward to 2015, I was sitting in my pharmacology class in nursing school. It was the week of our chemotherapeutics lecture. I remember sitting there half feeling really fascinated by the topic because I aspired to be an oncology nurse, half zoning out because I was familiar with a lot of the drugs and side effects being discussed. Then the slide came up with the title “Long Term Side Effects.” About halfway down, a bullet point read “Doxorubicin – cardiac dysfunction, often seen approximately 5 years after completion of treatment.” I’ll never forget turning to my friend sitting next to me and jokingly whispered, “Well, guess I’ll have cardiac issues next year.”

In 2016, approximately 5 years after completing treatment, I joined my hospital’s Childhood, Adolescent and Young Adult Survivorship Program. I was asked to participate in a study that was looking at cardiac late effects. I accepted, remembering the slide from my pharmacology lecture. After a day’s worth of signing consents, labs, and scans I was well on my way to joining my first study.

About a week later, I received a call from my doctor who runs the survivorship program. He explained to me that the baseline data they had gathered for the study showed my heart function to be too low and that I would need actual treatment – I could not risk falling into the placebo group of the study. My echo showed my left ventricular ejection fraction to be 42%.

I have been mildly symptomatic with my cardiomyopathy. I will intermittently have episodes of heart palpitations, and some shortness of breath here and there. I recall going to my first cardiology appointment, walking into the waiting room, and realizing I was the youngest person by at least 30 years. In meeting with the cardiologist, I was prescribed 3.125 mg of carvedilol to be taken daily and sent away, only advised to return in 6 months. I took the carvedilol as prescribed and suffered through the side effects due to having low baseline blood pressures. I found myself fatigued, dizzy, and lightheaded. I’ll never forget having to run out of a patient’s room during my nursing clinicals because I was starting to see stars. I ran to the nutrition room to shovel saltine crackers into my mouth, hoping it would increase my blood pressure. One of my fellow classmates came and took my blood pressure, it read 76/45...no wonder I was feeling so terrible. I continued this trajectory for the full six months. I returned to the cardiologist for follow up, told him about my concerns with the medication and how bad it was making me feel. He told me to just make sure I stay hydrated, always keep salty snacks with me, and continue the medication. I blindly complied, not knowing there were any other options, and suffered for an additional six months.

It was at this time that I finally reached out to my survivorship doctor who referred me to another physician at a different facility. This cardiologist showed me a sense of urgency, he wanted to do serial echocardiograms every 3 months, change my medication to an extended-release beta blocker in hopes of not having the drastic blood pressure drops, and potentially add in an ACE inhibitor if there wasn’t any improvement on the echoes. Over the next few visits, we played around with dosing, added in the ACE inhibitor, and continued to monitor. My

ejection fraction improved to ~45% and has maintained ever since. The question remains that had the first cardiologist treated me more aggressively, would we have been able to save some of my heart function?

Another concern that was brought up during my initial appointment with the new cardiologist was whether or not I would be able to carry out my own pregnancy due to cardiac risk. My husband and I were then left to grapple with how to start our own family safely. Had there been treatments available to preserve my heart function during, or even after I completed my cancer treatment, I may not have even been faced with these questions. There would have been less risk to this life altering decision to fulfil my dreams of having a family. Cancer survivors, like myself, deserve to live long, fulfilling lives. There is a desperate need for preventative treatment, as well as treatment and guidelines to address cardiac effects after surviving cancer. As a childhood cancer survivor, I have had to manage the effects and lifelong ramifications of my treatment.

Mariah: Hello, my name is Mariah. I am 43 and I live in Wisconsin with my husband, Troy, and our Siamese cat, Isaac. In 1980, at the age of one, I was diagnosed with neuroblastoma, a type of childhood cancer consisting of a solid tumor. My tumor grew out of several levels of my thoracic spine, wrapped around part of my heart, pushed against my trachea and lungs, and occupied almost the entire right side of my chest. I had multiple surgeries, radiation treatments, and two years of a chemotherapy clinical trial that included Adriamycin, which is an anthracycline. Outdated therapeutics and the location of my tumor left me with around 100 different complex medical conditions and late effects. I also have a higher risk of developing 9 different types of secondary cancers, and I have had 48 surgeries, with most related to my cancer or late effects. Being an older, long-term survivor, I have learned about my late effects as I experienced them. Even when information became available, it was not really shared with us. I learned the most about my cancer and potential late effects through my own research and when I attended a 2 ½ hour appointment about five years ago with a radiation oncologist, who took the time to study my case, talk to my husband and I, and answer our questions.

Shortly after treatments were finished, my parents were informed that I could experience potential cardiac issues, due to the Adriamycin. This was only one of the very few late effects we knew about. We later found out that part of my heart was in the radiation field, and that could cause cardiac late effects, too. Thus, I had the “double whammy” of chest radiation and receiving an anthracycline, but I have always had a cardiologist and regular cardiac testing, such as EKGs and echocardiograms.

Aside from regular cardiac testing, my parents were also told when I was fairly young that it would not be the best idea for me to get pregnant, since pregnancy and childbirth are incredibly taxing activities on the heart and the Adriamycin could weaken the heart, even without previous symptoms. My treatments may have left me infertile and unable to get

pregnant anyway, but a high-risk OB-GYN also told us that I should never, under any circumstances, get pregnant, due to some of my current severe late effects because there would only be about a 2% chance that the baby and I would survive. There are a number of reasons why I should not get pregnant, including concerns for my heart, but not being able to have a child has been the most difficult late effect for me.

Other prevention methods to address potential cardiac issues are dietary changes and trying to eat healthier. Due to several GI issues and gastroparesis, my body cannot process certain foods and I am limiting red meat for fish and chicken. In addition, I am trying to eat healthier overall and practice portion control. Furthermore, I am and always have been a non-smoker, which is a huge benefit for my heart health!

I know that exercising is extremely important for heart health, but this is very difficult for me to do. I use a cane for walking and a wheelchair for longer distances because I have chronic, excruciating bone, muscle, and nerve pain in my back, neck, and cancer scar, as well as right leg weakness and numbness, so it is difficult for me to exercise. When I am able, I ride a recumbent bike and do physical therapy exercises, but I worry about not being able to exercise enough for my heart.

Due to my cancer treatments, I am at risk for cardiomyopathy, heart failure, heart valve issues, coronary artery disease, and abnormal heart rhythms. It would be wonderful to see a medication developed to delay the progression of cardiac late effects in childhood cancer survivors. The combination of this medication, and routine diagnostics and monitoring would be valuable for me and many others to help find and address cardiac late effects as soon as possible.

Given the prominence and importance of the heart operating properly, as well as my risk and the fact that my potential cardiac late effects are extremely critical health conditions, 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. I also know that it is important to have a variety of data, and I represent the older population of survivors. Overall, survivorship has been a difficult, frustrating, lonely journey for me, and since childhood, I have wanted to be studied to help improve the outcomes for younger and future survivors. Furthermore, I have been dealing with a substantial number of late effects with little to no control over the number and severity of them. Simply having access to this medication would be an incredibly powerful way for me to take control and fight back against potential cardiac late effects that could easily claim my life!

Written Comments

September 15

- Sometimes new drugs have evidence of a few percentage points improved survival but in fact have a higher toxicity level thereby their late effects will most likely be more severe. It is really important that risk analysis is done and patients enabled to be educated about their choices. (That point just got made by someone speaking). Thanks for a fantastic meeting. It's so important to do this and credit to the FDA for listening (providing they act!).
- 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 & care providers. We need to make these available to all families, and especially those most challenged to access: 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.
- We long survivors need to have teams of specialists to rely on who apply personalized but standard treatments though countries. There must be international teams working and sharing information, treatments and approaches. It's happening to me, survivors often need to beg attention from doctors, oncologist themselves while embarking in new secondary late effects (such as new cancers) and advocate for their rights, major attention to the particular condition as long survivors struggling with late effects. I would like to feel safe home without trying to collect info alone overseas to be brought to my oncologists to have certain preventing treatment done. In Italy I was refused a preventive double mastectomy and I have to live in fear because of coming treatments and remaining breast. Thanks for trying to improve international exchanges.
- The following comments are informed by my experience as a survivor of NHL (dx age 5 yo, currently 51 years old and as a physician scientist, trained in preventive cardiology, epidemiology. 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 effect effectiveness of any of the above approaches
- I am really hopeful based on the hx of treatment modifications and results in decreasing frequency of cardiac effects at same time post dx (from CCSS papers) so far that primary prevention can decrease incidence. On the other hand I am concerned that trials of cardiac agents during primary cancer therapy may be showing falsely positive short-term results, but actually are not creating long-term positive changes to the heart, i.e preventing long-term damage. Please feel free to contact me with any questions

- Thank you to all the panelists and submitted videos. The doctors, nurses, and other providers listening are absorbing all of stories and learning important lessons. I know this forum is intended for patients and caregivers, understood if this comment is not shared.
- After relapse in 2010, I qualified for the Clofarabine 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.
- 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.
- 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 (56 yrs old now), 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.
- HL Survivor - I renounced to be a mother for the huge fear of putting my body under stress and danger again. So I went to a voluntary abortion in 2018 that I decided by myself mainly for this reason...Knowing that I developed BC today 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.
- When my childhood leukemia relapsed at age 20 I remember, vividly, my transplant physician plopping a stack of paper requesting I read it fully and sign it. I replied, "Just tell me which paper to sign." We went back and forth for at least 15 minutes. He expressed that because I was now over the age of 18 I had to understand the late effects of the treatment I was about to receive.
- I am a Hodgkin's survivor for 50 years now. I've had aortic valve replacement, via open-heart surgery, as well as a tricuspid procedure. I now suffer from AFIB. I was a marathon runner- completed 8 marathons over the past 40 years. I now have trouble walking, especially on an incline or going up stairs. I am not the person I used to be.
- I am a Hodgkin Lymphoma survivor and received Chemio+chest radiation in 1999 when I was 17. I developed BC (er+, Pr+, Her-2 negative) in 2022 after 23 years from treatments. Heart seems to be ok now but I need to start a hormone therapy and I am afraid how it could affect my heart and speed up any secondary effect. Thanks.
- Living with cardiac late effects after Leukemia, relapse, and stem cell transplant has been a huge factor in deciding not to pursue becoming pregnant. As someone who has always wanted to be a mother, it has been devastating.
- My daughter was on interferon.
- Teen Cancer America represents young people with cancer in the adolescent and young adult years. A common anxiety expressed is the fear of cardio late effects occurring and how to identify them. This commonly prevents them from undertaking physically demanding activities through a fear of the unknown. Therefore, research into risk assessment and the provision of remedial solutions for improving heart health would provide confidence and be welcomed by this community. Families of children that have been treated and young adults would like best practice established that required regular monitoring, testing and support. Furthermore, more investment in the emerging field of liquid biopsy that will enable earlier diagnoses and identify predispositions to late effects would be appreciated.

- For those with borderline cardiac function will it help to add ACE inhibitors?

Post-Meeting Submitted Comments:

- Cardiac issues are a very real concern for some of our survivors. And once diagnosed with issues, our survivors have a very difficult time reconciling their situation in order to be more like their peers, which is a natural part of the maturation process. For our men in particular, who want to take part in sports/fitness activities, limitations for cardiac care impress upon the type of life they are trying so hard to achieve. In so many ways, side effects take small pieces of the lives our survivors are designing for themselves. My son had already lost the ability to play soccer because he couldn't hear the chatter on the field with profound loss. The hearing, which progressed to profound, was threatening his ability to play musical instruments and he was being advised at 14 yr to stop playing to preserve what little hearing he had left. He had GI issues, was just diagnosed with chemo-induced ADHD, and progressive cognitive issues affected his ability to reason and remember in school. So when the cardiomyopathy was diagnosed six months later, my son struggled to recover from one more huge diagnosis and its impact on his life. Combined with other concerns, he couldn't lift weights. The heart issues resulted in huge swollen ankles, and his skateboard friends were very concerned for him, and were nervous to skate with him. For a teenager who was already on home/hospital care because of migraine clusters, the minimal "quality life" my son had was once again being whittled away further by another serious diagnosis, more rules, and "protection of his health" which basically just told him he couldn't do things he wanted to do. 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 concern and developing modified treatment to be gentler on the heart while still attacking the tumor. The stress/worry of struggling like an older relative our survivors are watching certainly crystalizes the reality of a compromised life for our survivors. Josh would respond emotionally, every time his father would return to the hospital, partially out of worry for his grandfather and partially out of worry that next time it could be him. Without the appropriate psychosocial support, this can make far too real how precarious life is for our survivors, and lessen a survivor's fragile confidence in a healthy future. 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.

- 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. Copied section: "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:"
- This is Dr Laurel Steinherz. I am thrilled to be watching this important program. I became the Pediatric Cardiologist at Memorial Sloan Kettering Cancer Center in 1977, just 5 years after the introduction of chemotherapy with Doxorubicin. The occurrence of acute post anthracycline cardiotoxicity was beginning to be reported and I soon discovered patients who had appeared to recover from cardiotoxicity, becoming symptomatic again a few years later. I began to suspect that there might be a more prolonged effect of the anthracyclines and decided to start screening patients who had completed chemotherapy with echocardiography, then a new modality introduced by my predecessor Dr Angela Gilladoga to evaluate heart function in Pediatric patients. This made me quite unpopular, since no one wanted to believe there were serious problems ahead for patients surviving their cancers. To my dismay, I found that about 25% of patients had abnormalities of systolic function. I published these findings in a series of patients screened, in the Proceedings of ASCO in 1984. Unfortunately, over the next years, I found that the toxicity was progressive. Over the next 40 years I attempted to alert the medical world to this late effect and to ameliorate the problem by exploring different anthracycline analogues, different method of administration, effect of healthier life styles, and protective agents such as Dexrazoxane. I tried treatment of patients with late cardiotoxicity in the 1980s with Hydralazine afterload reduction along with conventional CHF therapy. I later participated in studies of ACE inhibitors in patients with CHF and in asymptomatic systolic dysfunction to delay or prevent onset of symptoms. Of course I later incorporated Carvedilol into therapy. I participated in CCG and COG and published in 1992 the Guidelines for monitoring of pediatric patients

during therapy to limit toxicity and after chemotherapy to identify sub clinical toxicity allowing interventions. I am so glad that the problem is being acknowledged in this Program and most anxious to hear what further progress has been achieved. Thanks so much.