BEYOND SURVIVAL

Cancer treatment takes a toll on small bodies. As more children survive the disease, there's a push to better their health in the years ahead

By **Jennifer Couzin-Frankel**

More than 30 years ago, a new kind of patient began to appear in the cardiology clinic at Boston Children's Hospital: young people whose cancer treatment first saved their lives and then threatened to kill them.

Steven Lipshultz, a bespectacled pediatric cardiologist, examined them. They ranged from preschoolers to young adults, and all had recovered from leukemia, lymphoma, or other cancers. They were new to Lipshultz for a reason: Until recently, most children with cancer died.

But in the 1980s, a medical miracle was in the making. Clinical trials had pointed to combinations of drugs and radiation that could rescue once-doomed children. Survival rates, in the single digits for leukemia in the 1960s, surged past 50% and kept climbing. Oncologists and families celebrated the formerly unimaginable: birthday parties, high school graduations, a life relieved of terrible stress and fear. "Children were told they're free and clear, they're cured," says Lipshultz,

PHOTO: SETH DIXON/ST. JUDE CHILDREN'S RESEARCH HOSPITAL

Kiri Ness of St. Jude Children's Research Hospital tests the leg strength of brain cancer survivor Isaac Walsh, now 21.

now at the University at Buffalo, part of the State University of New York system.

However, he discovered they no longer had cancer, but they weren't healthy, either. Chemotherapy and, for lymphoma survivors, radiation used to shrink chest tumors had weakened hearts in ways he didn't fully understand. Anywhere from months to more than a decade after treatment, they trailed into Lipshultz's waiting room, frail and struggling to breathe.

Those young people were among the first to sound the alarm that pediatric cancer treatment could have grave aftereffects. Some, such as those Lipshultz cared for, suffered from abnormal heart rhythm or heart failure. Others ran into a slew of health problems: a second cancer caused by treatment for the first, infertility, trouble learning, thyroid abnormalities, impaired lung function, kidney disease. As more children survived, more doctors learned just how high the price of survival could be.

A single patient could spark the awakening. Years ago, Lisa Diller, a pediatric oncologist at the Dana-Farber Cancer Institute in Boston, was horrified when she encountered a man in his 30s dying of stomach cancer, a disease almost certainly caused by radiation treatment he received as a teenager for Hodgkin lymphoma. "What the heck is going on here, and what are we going to do about it?" she recalls thinking.

Today, cure rates for two common childhood cancers, Hodgkin lymphoma and standard-risk acute lymphoblastic leukemia, are more than 90% in the United States and Canada; overall, 83% of childhood cancer patients become long-term survivors. But in a 2014 study, 80% had at least one serious, disabling, or life-threatening health condition by age 45. Physicians and researchers are increasingly learning how cancer treatment reshapes the growth and development of small bodies into adulthood and beyond. As knowledge builds and the survivor population expands—it's now approaching 500,000 in the United States—a burgeoning effort is underway to blunt the effects of cancer therapy.

To understand the genesis of late effects of cancer treatment and how best to prevent and treat them, scientists are casting a wide net. They are studying drugs in zebrafish, walking mice with cancer on a treadmill, probing the cells of survivors, and testing DNA of newly diagnosed children. And in every lab, in every conversation with a family, scientists and physicians are walking a tightrope: Their greatest fear is jeopardizing a child's survival from cancer, but they're also striving to ensure good health in the decades to come.

"I remember laying in bed thinking, 'There's got to be a better way to do this,'" says Gregory Aune, a pediatric oncologist at the University of Texas Health Science Center in San Antonio, who runs a lab studying how chemotherapies harm the heart. Aune was 16 when he was diagnosed with Hodgkin lymphoma. He lost 30 kilograms during treatment. In the years that followed, he experienced thyroid problems and underwent triple bypass heart surgery at 35. Despite treatment-induced infertility, he now has two pairs of twins born from sperm he banked before chemotherapy and radiation. Cancer was "presented to me as, 'Just get through the therapy, and this will be over and [you] go back to normal.'" Instead, Aune says, "Your life trajectory changes. That's one of the things we have to change about oncology."

KIRI NESS FIRST ENCOUNTERED childhood cancer survivors en masse at St. Jude Children's Research Hospital in Memphis, Tennessee, after taking a job there in 2006. A physical therapist and epidemiologist, Ness knew that roughly one-third of survivors developed a second cancer by age 50, likely because of DNA damage to healthy cells during treatment; almost 10% had an underactive thyroid; and about 15% had heart dysfunction. Survivors who received radiation to the brain were less likely to be employed as adults than survivors who hadn't needed that treatment. Children who endured a bone marrow transplant were at especially high risk of complications, including infertility and kidney failure.

Ness wanted to meet survivors to better understand those long-term effects. St. Jude monitors several thousand survivors for life, and one after another streamed into her "human performance lab," set up to assess their general health. Ness was startled. "They look like old people," she remembers thinking about the adults in their 20s, 30s, and 40s. "They have wrinkled skin, they walk slowly, they're weak, they have characteristic gait patterns that mostly elderly people have."

The inside mirrored the outside. Results from cardiac stress tests and muscle strength assessments were "similar to [those of] people in their 70s and 80s," Ness says. Her reaction was identical to Diller's. "I was like, 'What is going on?'"

Ness started to investigate. The youngsters lost muscle mass during cancer therapy, she found; after treatment ends, "it seems like they don't ever become robust again." Years later, their nervous systems might slow down: Reactions became more sluggish, and they lost cognitive function. In 2013, Ness and colleagues reported that of 1922 pediatric cancer survivors with an average age of 33, about 10% qualified as frail. Another 30% were "prefrail," with some loss of endurance and muscle mass. The proportions mirror those in people older than 65.

For Ness, the roots of that rapid aging start with a truism of cancer treatment: While killing cancer cells, chemotherapy and radiation damage many healthy cells, too. Damaged cells often enter senescence—cellular old age—as a protective mechanism that allows them to expend less energy. From the results of cell aging studies, Ness speculates that in childhood cancer survivors, senescent cells "communicate with other cells around them," telling those cells to senesce as well. Those "aged" cells also emit molecules that cause low-grade inflammation in the body, which is linked to aging in healthy people.

Ness and colleagues are studying markers of biological aging; one, a protein called p16, is typically undetectable in

healthy young adults. But the researchers are finding it in the blood of some young adult survivors—suggesting their cells may be following a trajectory similar to that of much older people.

Kristopher Sarosiek, a cancer biologist at the Harvard T. H. Chan School of Public Health in Boston, is exploring a different link between cell damage during treatment and lasting debility. As a postdoc, he studied a form of cellular self-destruction called apoptosis. In healthy adults, cells were resistant to it, even when damaged. But in the developing tissues of healthy young mice, he found, "The apoptosis pathway is blowout high and incredibly active."

The reason? Young mice—and young children—are growing, and their bodies must wipe out any newly generated cells that are dysfunctional. Apoptosis accomplishes that. Anticancer treatments activate apoptosis in cancer cells—but also in healthy developing tissues, putting young cancer patients at high risk of tissue damage. Sarosiek points to a classic example: radiation to the brain. "You can give radiation therapy at very high levels to adults in the brain," he says, "and they'll experience slight neurocognitive damage. But if you do the same to a very young child, you can devastate their cognitive ability." Sarosiek is now trying to understand, in a mouse model of radiation treatment, how pediatric cancer therapy activates apoptosis in healthy tissues.

Whatever causes it, losing healthy cells during treatment can have a long-delayed impact, as Lipshultz's decades of work have shown for the heart. In various studies, he found that children treated with a popular class of chemotherapy drugs called anthracyclines suffer a loss of heart muscle cells that can initially cause few or no symptoms. But over time, the muscle loss becomes a problem. The heart grows by stretching its existing muscle cells, not by making new ones. Once those children reach adulthood, "the mass of the heart is inadequate for the size of the body," Lipshultz says. He has also found that some survivors experience a thinning of the walls of their heart or irreversible damage to heart muscle, further stressing the organ.

Most striking, however, is the gulf in outcomes. "I have some childhood cancer survivors 30 years out who have totally normal hearts," Lipshultz says. "I have others who died from therapy or needed a new heart."

TODAY'S GOAL is to carve a different path for the next generation of cancer survivors—to ensure that they do not end up, years later, in the care of doctors like Lipshultz. "We're not going to *not* treat cancer," says Bruce Carleton, a clinical pharmacologist at the University of British Columbia in Vancouver, Canada. But knowing which children treatment is likely to hit hardest could help doctors minimize its effects.

At Carleton's hospital, treatment causes permanent hearing loss in 37% of children with cancer—an outcome that forever alters how a 2-year-old learning to talk understands and communicates with the world. In the mid-2000s, Carleton launched a DNA hunt for gene variants that can raise or lower the risk of hearing loss and heart problems from chemotherapy. For hearing loss, he identified three variants; for heart problems, he found three more. In 2014, as part of a study, he and colleagues began to offer testing to all newly diagnosed cancer patients at British Columbia Children's Hospital, steps away.

One was 13-month-old Aeson Moen, whose cancer created an agonizing choice. He came to the hospital from a town more than 4 hours' drive east, and he had a large mass next to his spine, behind his heart. The diagnosis: high-risk neuroblastoma, a deadly childhood cancer. Aeson needed radiation—which would surely hit his heart as well—along with many doses of heart-hazardous anthracyclines.

But then genetic testing flashed a warning. The toddler carried two gene variants for anthracycline cardiac toxicity, which Carleton's lab calculated meant an 89% chance of severe heart damage; radiation would only ratchet up that number. Aeson's risk was alarming, says his pediatric oncologist, Rod Rassekh. "We were especially worried about him."

Rassekh had never treated a neuroblastoma patient like Aeson without anthracyclines, but he began to wonder whether he should jettison them. He and colleagues found an alternative protocol from Europe: a single dose of anthracyclines combined with other chemotherapies and radiation. Even that one dose, though, might be enough to push Aeson's heart into failure. "It made me feel more comfortable to leave that drug out than give it to him," says his mother, Ana Moen.

The hospital sought counsel from an ethicist. Ultimately, all agreed that Aeson's parents, with Rassekh's guidance, were making an informed decision. Aeson received anthracycline-free treatment, though it was hardly easy: He still endured many rounds of other chemotherapies, radiation, and a stem cell transplant. "Was I nervous, as his oncologist?" Rassekh says. "I was extremely nervous, thinking, 'Are we making the right decision?'"

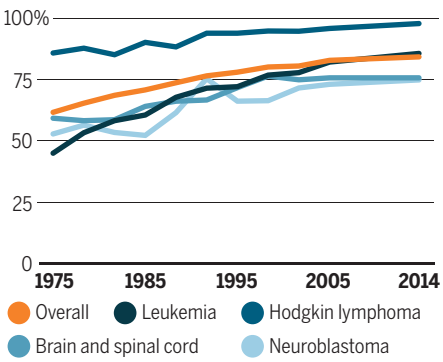
More than 4 years later, Rassekh is beginning to exhale. Aeson started kindergarten last fall and will turn 6 next month. He is now cancer-free with a perfectly healthy heart. His first season of T-ball begins this spring.

"When I first started, I thought every family would want all the chemo, period," to maximize the chance of a cure, Rassekh says. But he's learning that many families are willing to forgo some treatments if doing so means better odds of good health. Rassekh recalls a 4-year-old he treated more than a decade ago for neuroblastoma, before the genetic testing was

From hopelessness to hope

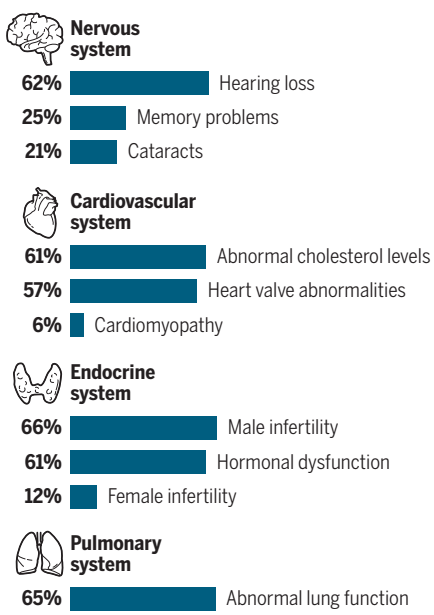
Childhood cancer was once a death sentence, but today more than 80% of children and teenagers survive long term. This graph shows survival rates depending on the year a young person was diagnosed.

Survival 5 years after cancer



After the cure

Adults who survive cancer as children can suffer long-term health effects. One study of 1700 people ages 18 to 60 explored how treatments toxic to an organ system—chemotherapy, radiation, or both—led to problems in the years ahead. The bars show the frequency of certain complications.



CREDITS: (GRAPHIC) N. DESAI/*SCIENCE*; (DATA) NATIONAL CANCER INSTITUTE SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS PROGRAM; M. HUDSON *ET AL.*, *JAMA* 309, 2371 (2013)

available. Reviewing her case, he found that she carried the same gene variants as Aeson. One year after treatment, the girl needed a heart transplant—and when the first transplant failed, she needed a second.

This year, Carleton is expanding gene testing to nine more children's hospitals across Canada. Other major gene sequencing efforts are underway. One of the broadest is through the pioneering Childhood Cancer Survivor Study (CCSS), which launched in 1994 and includes more than 25,000 survivors of childhood cancer diagnosed from 1970 to 1999 in the United States and Canada. By the end of the year, the CCSS will have sequenced the exomes—the protein-coding DNA—of more than 8000 of them, says Greg Armstrong, a pediatric neuro-oncologist at St. Jude and lead investigator of the CCSS.

Changing a treatment protocol, as doctors did for Aeson, isn't always possible. More than 4000 kilometers from Vancouver, a collaborator of the British Columbia group is weighing other uses of genetic results. "We're not going to get rid of the anthracyclines" for everyone, says Jason Berman, a pediatric oncologist at Dalhousie University in Halifax, near Canada's eastern edge, "but maybe we'll have protective drugs" to give alongside them, particularly for patients genetically prone to the toxic effects.

When he's not caring for children with cancer, Berman runs a zebrafish lab and uses the small tropical fish to screen dozens of potential drugs. So far, he has hit on two that, when given with anthracyclines, protect a fish's heart from damage without dulling chemotherapy's effect on cancer cells. As his own hospital prepares to take up Carleton's gene testing regimen, Berman envisions eventually testing new protective compounds on the children deemed at highest risk of heart damage.

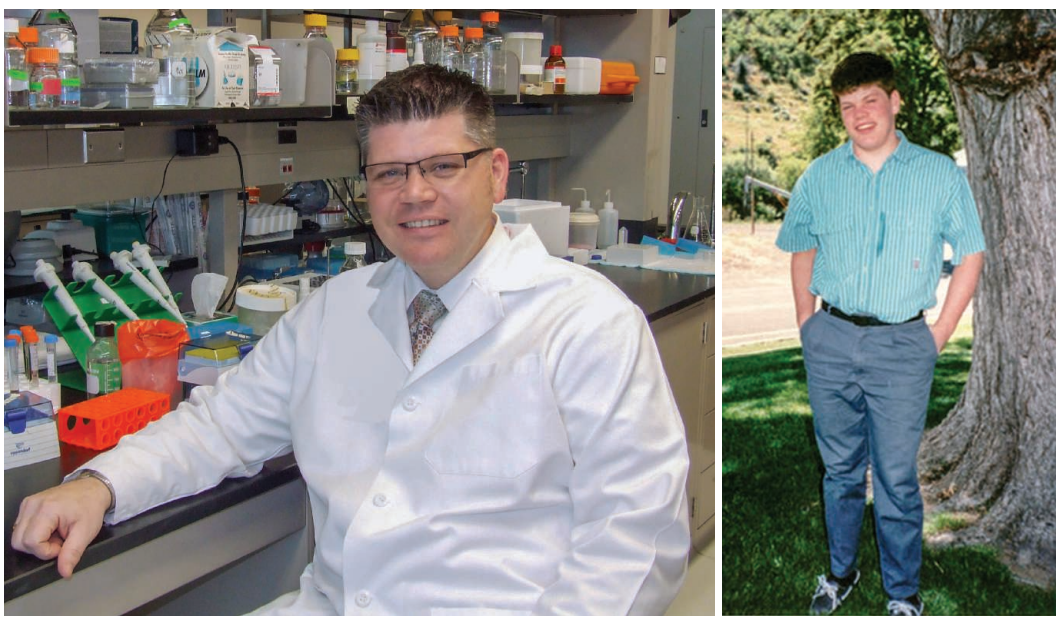
One such drug is already available: dexrazoxane, which is approved in the United States to minimize cardiac damage in patients with breast cancer and sometimes offered to children receiving cancer treatment. Lipshultz pioneered testing dexrazoxane with pediatric patients in the 1990s. Now, physicians are studying how well dexrazoxane heads off cardiac problems years after treatment. Lipshultz, pediatric oncologist Eric Chow at the Fred Hutchinson Cancer Research Center in Seattle, Washington, and others are tracking down hundreds of adults who received dexrazoxane during those early trials.

Some researchers wonder whether ordinary exercise might safeguard the heart. At the University of Texas MD Anderson Cancer Center in Houston, pediatric oncologist Eugenie Kleinerman is considering whether brisk walks during treatment can protect cardiac function in young people with the bone cancer osteosarcoma. Like many in the field, she has a tragic story that set her on this path: Kleinerman cured a young woman of sarcoma only to learn that she'd collapsed and died from an apparent heart attack on a Michigan college basketball court years later. A self-described exercise nut, Kleinerman created a mouse model of osteosarcoma treatment in which the animals sustain heart damage from doxorubicin, an anthracycline drug. While getting twice-weekly chemo infusions, they're put on a treadmill for a brisk 45-minute walk. Echocardiograms and autopsies revealed that, immediately after chemotherapy and 2 months later, mice that exercised had hearts indistinguishable from those of animals that hadn't gotten chemotherapy, Kleinerman reported in April 2018 in the *Journal of Pediatric Hematology/Oncology*.

Late last year, she launched a pilot study to determine whether an exercise program is feasible for adolescent and young adult osteosarcoma patients, who often have leg tumors. If it is, Kleinerman says she hopes to launch a larger trial to test whether the strategy can keep hearts healthy.

Some pediatric oncologists see a field on the cusp of change. Their toolkit—largely from the 1980s and earlier, because new treatments are almost always designed for adults—is finally expanding. Novel targeted therapies and immunotherapies may have fewer, and certainly different, long-term effects. Meanwhile, clinical trials have helped pinpoint patients at lower risk of relapse or death; such children can sometimes be spared some hazardous therapy. Even for the childhood brain cancer medulloblastoma, among the most aggressive cancers, scientists are testing whether one low-risk group can safely decrease radiation. In 2016, Armstrong and CCSS colleagues reported in *The New England Journal of Medicine* the tangible effect of gentler treatment: Twelve percent of children who survived any cancer in the early 1970s died within 15 years of diagnosis, compared with 6% treated in the early 1990s.

At 45, Aune still lives with the effects of cancer therapy. Recently, he found himself peering through a distorted mirror: In front of him sat a girl the same age he was at diagnosis, 16, with the same burden of Hodgkin lymphoma. And yet her trajectory would be different. She endured 3 months of treatment to his 9. She quickly returned to school full-time, whereas he needed an extra year to graduate. She avoided chest radiation, thanks to clinical trials more than a decade ago suggesting that most Hodgkin patients don't need that brutal treatment—which left girls like her with a one-in-three chance of breast cancer by their mid-40s. "She's going to do really well," Aune predicts. Now, he says, it's up to him and others to create a future as bright for the survivors still to come. ■



Diagnosed with Hodgkin lymphoma as a teenager, Gregory Aune went on to study the aftereffects of chemotherapy.

PHOTOS: (LEFT TO RIGHT) DAVID RODRIGUEZ; JANE AUNE

Beyond survival

Jennifer Couzin-Frankel

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