

# S T A N F O R D M E D I C I N E

Fall 2017

special report

## SPOTLIGHT ON KIDS

### Holistic healing

Families and nature are central for the new Lucile Packard Children's Hospital Stanford

### Zapping tumors

The promise of focused ultrasound treatment

### Immersed in care

Easing anxiety with virtual reality

### No place to call home

How a housing crunch puts health at risk

### Hide and seek

Finding, killing elusive cancer cells in children

### Saving children

A conversation with Helle Thorning-Schmidt

plus

### Climate health

Our environment's making us sick

### Natural solution

Leading the way in aortic valve repairs



S T A N F O R D  
M E D I C I N E

Fall 2017



# PERFECT TIMING

## THE KEY TO PREGNANCY CLOCKWORK

Pregnancy usually lasts nine months, but until recently it's been a mystery why. Now researchers have discovered that meticulously timed changes in pregnant women's immune responses are an important key to keeping their babies from arriving too early. The findings, which were published Sept. 1 in *Science Immunology*, reveal that there is an immune clock of pregnancy and suggest it may help doctors predict preterm birth.

Immune changes are a normal part of pregnancy, designed to protect a woman's body from rejecting her fetus, but previous data suggest that related inflammation could trigger early labor. A group of researchers at the March of Dimes Prematurity Research Center at Stanford wanted to examine the characteristics of the changes, in

terms of both timing and immune properties, that are present as women progress through pregnancy.

Almost 10 percent of babies born in the United States are born too soon. They face a range of risks that include respiratory problems, eye disease, deafness, brain injury and death.

"It's really exciting that an immunological clock of pregnancy exists," says the study's lead author, Nima Aghaeepour, PhD, instructor in anesthesiology, perioperative and pain medicine. "Now that we have a reference for normal development of the immune system throughout pregnancy, we can use that as a baseline for future studies to understand when someone's immune system is not adapting to pregnancy the way we would expect."

For the study, researchers used mass cytometry, a technique developed at Stanford, to simultaneously measure as many as 50 properties of each immune cell in the blood samples from 18 pregnant women who had full-term babies. The samples were taken at various times for each woman — once during each trimester of pregnancy and once six weeks after their babies were born.

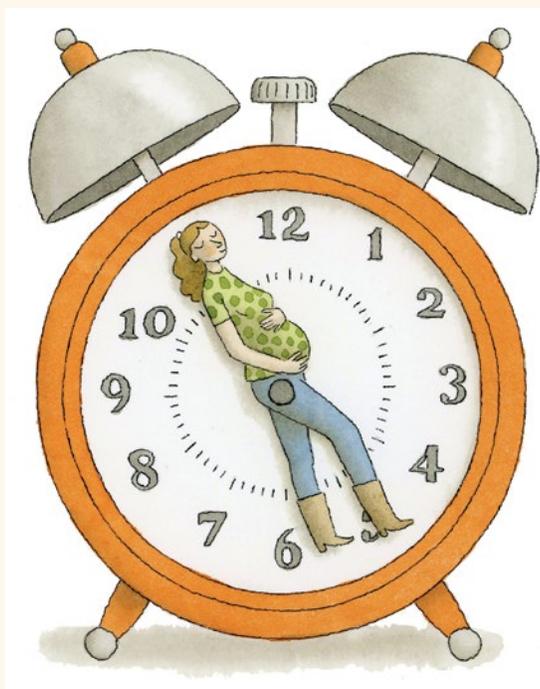
The data were then analyzed using an advanced statistical modeling technique, which was introduced with this study, to detail immune system changes throughout pregnancy.

"This algorithm is telling us how specific immune cell types are experiencing pregnancy," says the study's senior author, Brice Gaudilliere, MD, PhD, assistant professor of anesthesiology, perioperative and pain medicine.

"The immune system does not act in isolation, and we're now very interested in profiling its interplay with other aspects of mothers' biology, such as their genetics, metabolism and the body's microbial communities to come up with a holistic biological clock of pregnancy," Aghaeepour adds.

The next step, the scientists say, is to conduct similar research using blood samples from women who deliver their babies early, to see whether their immune functions were different. "We're especially interested in understanding more precisely what is happening very early and very late in pregnancy," says Gaudilliere. "Ultimately, we want to be able to ask, 'Does your immune clock of pregnancy run too slow or too fast?'"

The hope is to identify which immune properties are present in women who go on to deliver early and to design a blood test to detect them. — ERIN DIGITALE



# S T A N F O R D M E D I C I N E

SPECIAL REPORT

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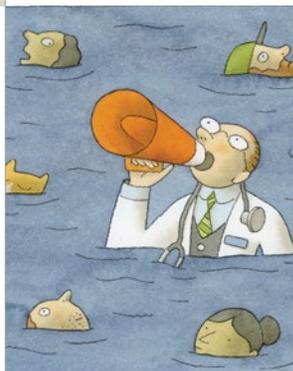
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# letter from the dean

**As anyone who's spent any time with children can tell you, kids are different — and they keep changing. From a medical perspective, they're different too: Their physiologies and experiences are distinct from those of adults, which often means they are especially challenging patients to treat.**

Their care calls for special tools and strategies, and is most likely to succeed in a special place: an academic medical center where the brightest minds come together for the sake of children's health.

In this issue of *Stanford Medicine*, we're celebrating pediatrics and marking the opening of the expanded Lucile Packard Children's Hospital Stanford, the place where Stanford Medicine faculty and trainees provide unsurpassed care for sick children, teach the next generation of pediatricians and scientists, and conduct clinical and translational research that will transform child health around the world.



Through close collaboration, Stanford Medicine researchers and clinicians routinely bring medical advances from their laboratories to the benefit of our pediatric patients. For example, Gill Bejerano, PhD, and his colleagues recently used machine learning to devise an automated approach for diagnosing rare congenital diseases in children that keeps nearly all genomic information private. At Packard Children's, Dr. Bejerano put his team's innovation to work, offering the comfort of a diagnosis to previously undiagnosed patients while helping to usher in an era where genomes can be both utilized and truly protected.

In this magazine, you'll read more about how our researchers and clinicians are working together on behalf of pediatric patients everywhere. Young leukemia patients are now receiving treatments, pioneered by Stanford pediatric cancer specialists, that use their own immune system to fight their disease when other treatments have failed. Certain tumors are even being zapped with high-intensity focused ultrasound, thereby reducing their size without the harmful side effects of the other options. The expanded Packard Children's will include a dedicated pediatric facility for this promising ultrasound technology that until recently was used almost exclusively to treat adults.

By providing predictive, preventive and precise care, Stanford Medicine is delivering precision health to our youngest patients. But precision health is not just high-tech, it's also high-touch, focused on the patient experience. Since medical care can be particularly stressful for children, Stanford Medicine faculty are exploring new ways to ease pediatric anxiety and maybe even provide some fun by creating virtual reality games that distract and calm children before and during medical procedures.

For a seriously ill child or a clinician or researcher who cares about children's health, it's hard to think of anywhere better than Stanford Medicine. It's a special place that puts kids first by conducting ground-breaking research, training future leaders, and delivering compassionate and unsurpassed care.

Sincerely,  
Lloyd Minor, MD  
Carl and Elizabeth Naumann Dean of the School of Medicine  
Professor of Otolaryngology - Head & Neck Surgery

# upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

## Those aching bones

BEING SHORT MIGHT have been an advantage for early humans as they migrated from Africa to colder northern climates, but it could also be the reason arthritis is so prevalent today, according to developmental biology professor David Kingsley, PhD.

The very genetic variant that helped protect humans from such dangers as frostbite and broken bones by reducing bone length, also left them at greater risk of osteoarthritis, Kingsley points out.

He says geographic patterns suggest that animals adapt to colder temperatures and are better able to conserve body heat with more compact, round bodies and short appendages.

Similarly, research shows a link between the length of the neck of the femur bone and the likelihood of a hip fracture, making short bones less prone to fractures.



Research by Kingsley and colleagues at the School of Medicine and at Harvard University shows that although at least half of Europeans and Asians harbor the genetic variant linked to osteoarthritis, a painful joint disease that afflicts millions of people, the variant is relatively rare in African populations.

"Many people think of osteoarthritis as a kind of wear-and-tear disease, but there's clearly a genetic component at work here as well," says Kingsley, senior author of a study describing the research, published online July 3 in *Nature Genetics*.

More than 8,000 kilns are spewing deadly pollutants across Bangladesh, but Stanford researchers aim to convince kiln owners there and across South Asia to use cleaner technology. More at <http://stan.md/2fNiaU1>

## Expanding learning borders

STANFORD OPENED THE CENTER for Health Education this September to provide online training to health care workers, medical students and citizens around the globe.

Charles Prober, MD, former senior associate dean for medical education and a pioneer in advancing health education through digital training, will direct the center, a collaboration of the School of Medicine and the Office of the Vice Provost for Teaching and Learning.

The center will help "extend advances in understanding achieved by our world-class faculty to learners far beyond our campus boundaries," says the medical school's dean, Lloyd Minor, MD.

## Autism therapy promise

RESEARCHERS HAVE FOUND a clue for predicting whether a child with autism will benefit from treatment with oxytocin, sometimes called the “love hormone,” which is known to improve social behavior for some autistic children.

A Stanford study published online July 10 in the *Proceedings of the National Academy of Sciences* found that autistic children with low levels of oxytocin showed more improvement from oxytocin treatment — intranasal spray twice a day — than the other children studied.

Blood oxytocin levels might be a biological sign predicting who will best respond to the therapy, says Karen Parker, PhD, associate professor of psychiatry and behavioral sciences and lead author of the study of 32 children with autism.

“Hopefully, this is a first step to identifying the characteristics of people with autism who respond to specific treatments,” says Antonio Hardan, MD, professor of psychiatry and behavioral sciences and the study’s senior author.

A large trial of oxytocin for children with autism is underway at several institutions across the United States, and Parker and Hardan are curious about whether it will replicate their findings.

# Cloaking DNA

RESEARCHERS HAVE FOUND A WAY to better protect individuals’ privacy during genetic disease research by using cryptography to keep most of the genetic information hidden, exposing only genetic differences that are relevant to a particular disease.

The method could lead to better research of diseases that can be passed from generation to generation, researchers say.

“Often, people who have diseases, or those who know that a particular genetic disease runs in their family, are the most reluctant to share their genomic information because they know it could potentially be used against them in some way,” says Gill Bejerano, PhD, associate professor of developmental biology, of pediatrics and of computer science and a senior author of the research published Aug. 18 in *Science*. Co-senior author is Dan Boneh, PhD, professor of computer science and of electrical engineering.

The “cloaking” method enables someone whose genome is being studied to encrypt it, using an algorithm on their computer or smartphone, into a linear series of values describing the presence or absence of the gene variants and allowing researchers to pinpoint only study-relevant variants.



## HEALING OUR HEALERS

TAIT SHANAFELT, MD, A PIONEER in physician burn-out research and prevention, has been named Stanford Medicine’s chief wellness officer, one of the first at a U.S. academic medical center.

Shanafelt comes from the Mayo Clinic, where he led an initiative to counter burnout and improve physician well-being. His focus on physician wellness began in 2001 when he published a groundbreaking study that launched a national conversation about the problem and its impact on care.

The burnout trend, Shanafelt says, is “eroding the soul of medicine.”

Thousands of doctors in surveys Shanafelt has overseen report that they are emotionally exhausted, have lost meaning in their work or don’t feel engaged with patients. The impact, his studies reveal, can be more doctor errors, higher hospital patient death rates and less compassionate care.

Shanafelt, who started Sept. 1, will direct Stanford’s WellMD Center, the core of its physician wellness program; will serve as associate dean of the medical school; and will continue clinical work and research on treatments for people with chronic lymphocytic leukemia.

## Dear old dad

A RECENT STANFORD STUDY shows that the percentage of newborns in the United States whose fathers are older than 40 nearly doubled between 1972 and 2015, a trend with both positive and negative implications.

Older dads likely will be more involved in child-rearing, and have higher levels of education, better jobs and more resources.

But genetic mutations in sperm as men age mean there are “associations between older fatherhood and higher rates of autism, schizophrenia, chromosomal abnormalities, some pediatric cancers and certain rare genetic conditions,” says Michael Eisenberg, MD, assistant professor of urology and senior author of the study, published online Aug. 30 in *Human Reproduction*.

Eisenberg also notes a steady increase of the average age of U.S. dads of newborns from 27.4 years old to 30.9.

“Chronic fatigue syndrome is by no means a figment of the imagination. This is real.”

JOSE MONTOYA, MD



## No longer a question

THE CAUSE OF CHRONIC FATIGUE SYNDROME has baffled researchers for decades, leaving patients to suffer a frustrating array of symptoms so varied it's difficult to diagnose and treat.

But a recent study shows a connection between inflammation and the disease, offering promise for future diagnostics, studies, and potential clinical trials of immune-regulating drugs.

In 2004, Jose Montoya, MD, professor of infectious diseases who oversees the Stanford ME/CFS Initiative, encountered his first patient with chronic fatigue syndrome and never forgot it.

“I have seen the horrors of this disease, multiplied by hundreds of patients,” says Montoya, lead author of the study published online July 31 in the *Proceedings of the National Academy of Sciences*. “It's been observed and talked about for 35 years now, sometimes with the onus of being described as a psychological condition. But chronic fatigue syndrome is by no means a figment of the imagination. This is real.”

He began exploring whether inflammation was key in diagnosing the syndrome after noticing the sporadic effectiveness of antiviral and anti-inflammatory drugs. He called in Mark Davis, PhD, senior author of the study, professor of immunology and microbiology, and director of Stanford's Institute for Immunity, Transplantation and Infection. Their teams analyzed blood samples from 192 of Montoya's patients and 392 healthy control subjects. Results showed certain biomarkers, some of which cause inflammation, were higher in patients with severe symptoms and lower in those with milder symptoms.

## Dessert?

### Skip it

Counting on how many calories your fitness device says you burned today to justify dessert? Pass.

New research shows that seven devices designed to track calories burned are “way off the mark,” says Euan Ashley, DPhil, senior author of a paper published May 24 in the *Journal of Personalized Medicine*. The worst-performing device was off by more than 50 percent; the best by an average of 27 percent.

But the news isn't all bad.

Heart rate tracking “performed far better than we expected,” with an error rate on six devices of less than 5 percent, says Ashley, professor of cardiovascular medicine, of genetics and of biomedical data science at Stanford.

His team used medical equipment to monitor 60 volunteers who wore fitness trackers — an Apple Watch, Basis Peak, Fitbit Surge, Microsoft Band, Mio Alpha 2, PulseOn and a Samsung Gear S2 — as they ran or walked on treadmills, or pedaled stationary bikes.

# I N N E R child

## THE HEART OF PEDIATRICS

*"It is hard to be brave when you're only a Very Small Animal," says Piglet to Rabbit in A.A. Milne's *Winnie-the-Pooh*.*

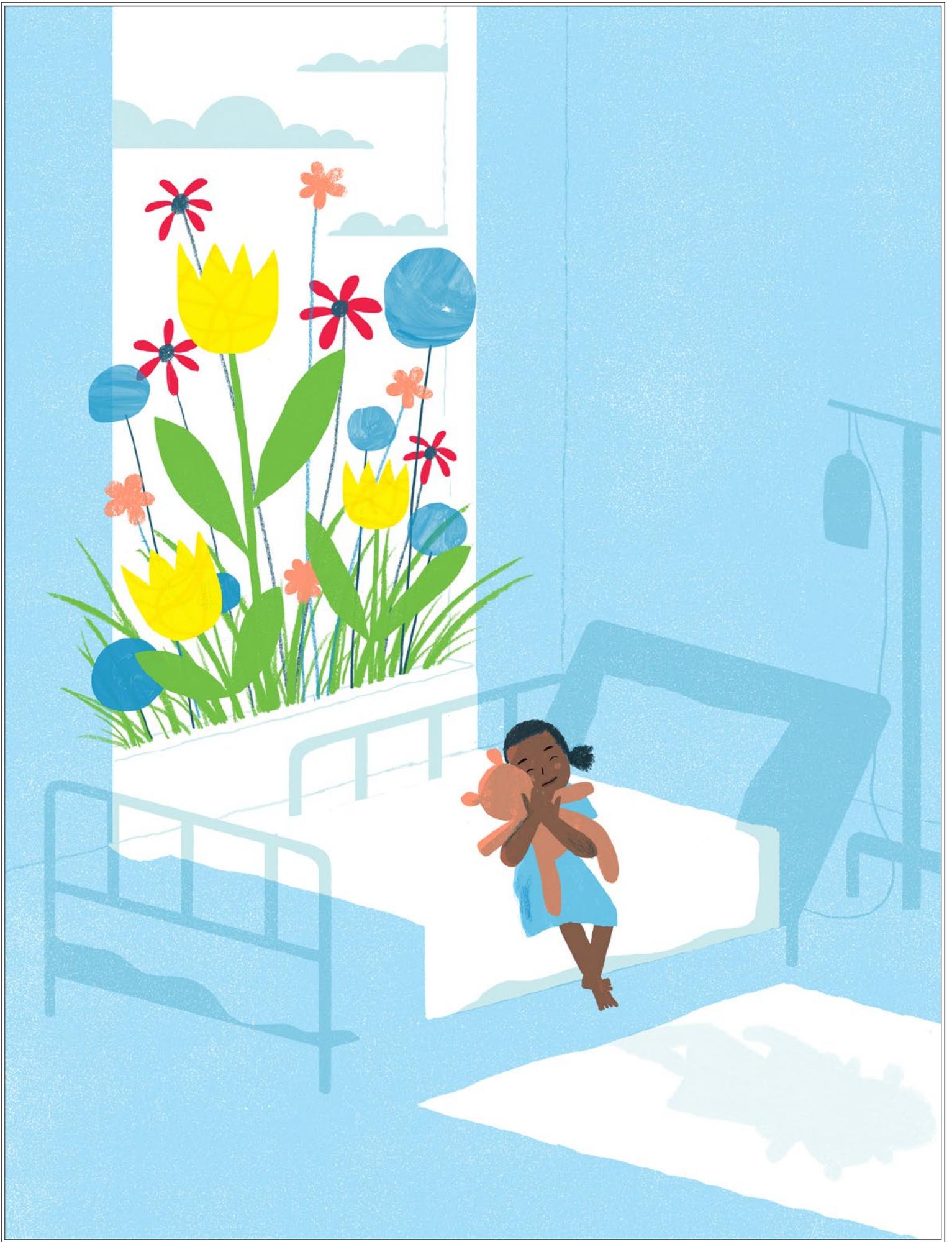
A similar conundrum is top of mind for many pediatricians: They know it's hard to be brave when you're only a Very Small Person, especially when you feel awful and need a shot or stitches, or have to stay in a hospital overnight. Children arrive at their care from a different perspective than adults do, making it essential to treat kids as kids, not as little adults. From using virtual reality to distract kids during treatments, to ensuring there's play space in hospitals, the trend is toward improving kids' care by helping them feel comfortable and safe.

Comfort, however, is only one factor. Specialists must consider what is best for children's developing bodies, and the lifelong implications of treatments they choose.

Immunotherapy treatments that fight cancer in adults, for instance, don't work on children's youthful immune systems, so researchers are reinventing them. And doctors are using a new technology — high-intensity focused ultrasound — that allows them to shrink certain types of tumors without surgery or the damaging side effects of the other treatment options.

To find out more about putting kids at the center of their care, read on.

ILLUSTRATION BY CHRISTOPHER SILAS NEAL



SPOTLIGHT ON KIDS

# a healing ENVIRONMENT

NEW CHILDREN'S HOSPITAL  
INCLUDES FAMILY  
AND NATURE IN CARE





When Diane Flynn's third child was born with a cleft lip in 2001, her family embarked on a series of six surgeries and appointments with dozens of specialists at Lucile Packard Children's Hospital Stanford that spanned eight years. For the Flynn's, the hospital became a second home.

It wasn't long before Flynn felt compelled to give back to the hospital that was so supportive of her family, so she contacted the director of the hospital's Family Advisory Council and became one of five parent leaders of the group, which provides firsthand feedback on everything from bedside care to food service.

**BY KATE DETREMPE**

PHOTOGRAPHY BY LESLIE WILLIAMSON

**IN A CORNER** of the new hospital's lobby is a digital display that runs nature-themed videos children can interact with just by moving their bodies next to the screen — by reaching toward the binoculars, for example.



Eight years later, in 2009, the hospital team that was starting to plan for a new children's facility wanted to gain an understanding of needs from the perspectives of a wider group. They created a design committee that included representatives from the project's two architectural firms, hospital staff, board members, faculty and members of the Family Advisory Council.

"About 10 years ago, before the design team or architects had plans, they had parents," says Flynn, who joined the committee as her son, Matthew, now 16, was spending less time in treatment. She wanted to be a voice for families like hers.

The committee's meetings became open forums for input and brainstorming about what they wanted to see in the new campus. "It didn't take long for us all to agree — a restorative space that felt light, healing, engaging," Flynn says.

That feedback about the ambiance and surroundings in the new space is present in nearly every aspect of the new building, which is just weeks away from its December opening. The building, which houses the medical community's most advanced medical tools, is meant to be responsive to changes in pediatric care as it evolves. But the guiding principle is for the facility to reflect a holistic approach to healing — focusing on the family at the heart of patient care and creating a restorative environment by integrating nature and art. The concept is reminiscent of Lucile Salter Packard's founding vision for the hospital: to nurture the body and soul of every child. She recognized the power of nature as an important part of healing. She wanted kids to be treated like kids — not just patients. And she believed that caring for a child involved the whole family.

#### FEELINGS MATTER

There is deep evidence that a hospital's physical environment and the well-being of patients and families are closely related. In 1984, two years before planning for the existing Packard Children's Hospital began, *Science* published a study by environmental psychologist Roger Ulrich, PhD, that was lauded as the first to use modern medical research to support the healing effects of nature, an approach he called "evidence-based design." Ulrich studied 23 gallbladder surgery patients who recovered in rooms with windows looking into a natural scene and 23 whose rooms looked out to a brick wall. He found that the patients with views of nature stayed in the hospital an average of one less day, had 3.5 times fewer negative comments from nurses, such as "frustrated behavior" or "upset and crying," and took fewer and weaker medications compared with the other patients.

"By the early 1980s, evidence supporting the stress-reducing effects of nature was so consistent, and we under-

stood that natural beauty's effects were much more than skin deep," Ulrich says. "I began to wonder where could this be useful, and the main answer surfaced at hospitals — a location where people are captive for a period of time if they're bed-ridden, where they are experiencing stress and pain, and for whom distraction facilitated by looking at nature might help improve recovery outcomes."

Now, he explains, it is routine for hospitals to be built to support a positive psychological experience for patients, but he points to the existing Packard Children's Hospital as "an early adopter" when it opened in 1991.

"It was one of the first hospitals I was consciously aware of that had explicitly used the emerging field of evidence-based design to inform the design," he says of the facility, which

MATTHEW FLYNN, A FORMER  
PACKARD CHILDREN'S  
PATIENT, AND HIS MOTHER,  
DIANE FLYNN, a Family Advisory Council  
member, seated on a "wolf head" in one of  
the hospital's gardens. Right: The lobby with  
construction nearly complete.





was acclaimed for having nature-based and family-centered themes, with terraces on each floor and a garden at the center.

Architects of the new building, which is connected to the existing hospital, took a similar approach by challenging the fundamental mindset of being inside a hospital, beginning with the experience of patients as they arrive. “A common issue in health care is that traditional hospital design places operating rooms and imaging services on sub-ground-level floors to accommodate heavy surgical and diagnostic equip-

ment,” says Robin Guenther of Perkins+Will, lead architect for the new building. Perkins+Will collaborated with HGA on the project. “In the last generation of hospital building about 30 years ago, people weren’t really crafting an experiential journey for patients. They were focused on accommodating the technology — hospitals for machines.”

But the practice of moving patients down into a basement level, she explains, can exacerbate feelings of fear or anxiety that patients — particularly children — experience prior to such “scary procedures” as surgery. Reflecting a shift away from this, the new hospital’s pedestrian entrance is at ground level, which is also the location of the treatment center (surgery, interventional services, imaging and nuclear medicine). Families don’t have to traverse below ground and instead enter the main lobby and have only a few choices about where to go next: up the staircase or elevator, or across the lobby into the surgery and imaging unit.

“From a patient experience perspective, it is revolutionary,” Guenther says.

The challenge is that the most public part of the new hospital — the lobby — is directly adjacent to the most private area — the surgical treatment center. To marry these spaces, lobby walls are lined with enclosed alcoves where families can



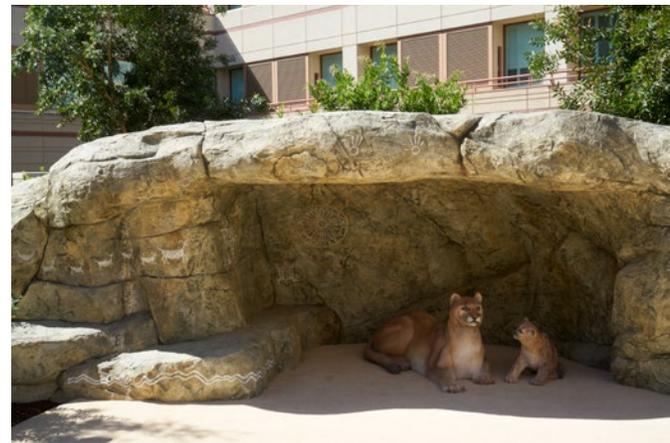
wait. On each ascending inpatient floor, open spaces contain wood-paneled niches that resemble treehouses to provide private spaces for those who seek it.

“What we heard from families is that when they aren’t in a patient’s room, they tend to gather in public spaces, rather than in waiting rooms behind closed doors,” explains Jill Sullivan, vice president of strategic space planning and general services.

Architects also wanted to reflect elements of Northern California’s native environment to provide a sense of being alongside nature as you move through the building, despite being in a hospital, Guenther explains.

Outside, 3.5 acres of gardens and green space surround the building, and inside, waiting areas have large picture windows. Each patient room has a planter box outside the window and a view to the gardens, and about 150 feet of the new cafeteria space is lined with glass doors that open to an outdoor dining patio overlooking a garden. The garden has native plants and animal installations that represent California’s eco-regions, including a puma den, a gopher’s burrow and a redwood tree fort.

Most uniquely, each of the building’s four patient care levels has two outdoor decks — one for patients and visitors, and one for staff.



“Patients, family members, visitors, even staff can be too pressed for time to travel down the elevator and search outside for a garden,” Ulrich explains. “To have a restorative, outdoor area on each floor is very important from the standpoint of ensuring easy access to nature and thus positively impacting patient health.”

Guenther says that, in the past, safety concerns prevented the construction of outdoor spaces on above-ground levels.

“The idea of outdoor space on nursing units is one where

IMAGE OF CHILDREN COURTESY OF PERKINS+WILL

Packard Children’s is at the beginning of a new curve in design,” she says, explaining that 6-foot-tall tempered safety glass panels enclose each deck to prevent people from falling. “It is a new generation of outdoor space that really is easily accessible to patients and families.”

The hospital’s use of natural light and focus on a holistic approach to healing is also embodied in the sanctuary space, which includes a private healing garden and access to a meditative labyrinth. The concept breaks a mold that was popularized during the increased secularization of health care beginning in the latter half of the 20th century, when design shifted from common cathedral-inspired hospital chapels to minimalistic spaces.

“In the last generation of hospitals, the idea of spiritual space became so minimal that it became a conference room. This hospital reintroduces a sanctuary space that is truly special,” Guenther says.

THE HOSPITAL IS DESIGNED TO EXPOSE PATIENTS, FAMILIES AND STAFF TO NATURE, with 3.5 acres of gardens and green space, large picture windows, and images and sculptures representing California wildlife.



As the new sanctuary was conceptualized, the team again called on the Family Advisory Council, whose members represent a variety of faiths (and non-faith), to build something that would appeal to many spiritual beliefs and backgrounds. The result “is a space that is multicultural, multidimensional and goes beyond religious practice,” Guenther says. “It is about recognizing that we are whole people who have physical bodies, minds and a spirit and we need to provide a place for people to keep in touch with that.”

## SWEATING THE SMALL STUFF

For patient rooms, architects took care to treat them as the center of a child's hospital experience, and not just a place for essential medical equipment and visits from clinicians.

Architects designed them to be healing, comfortable spaces for the whole family. Nearly all of them are private and more spacious to serve as home base for mealtimes, movies and games and include sleeping accommodations for two family members.

"When a parent can have a private room, their own space with their child, they can create a quiet and healing space," says Karen Wayman, director of the Family Advisory Council. "That's so important for a parent's relationship with their child."

To refine the rooms, full-scale detailed mockups were constructed in an off-site warehouse. Everything was in

to disturb him by turning on the overhead lighting to read, so for the new building the design committee made sure we would have cozy reading lights in each room."

Parents also championed having bathtubs in many of the bathrooms instead of standing showers to make bath time easier for little ones. Their input also resulted in the inclusion of a family lounge, laundry facilities and family kitchen on every patient floor to help families maintain day-to-day routines. "You just don't think about it until you walk it from a patient or parent perspective," Flynn says.

The collaboration between providers and parents was key, Wayman explains. "Providers learned about the parents' experiences in the hospital, and parents had an opportunity to see how things worked from the provider perspective," she says.

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place, including medical equipment, patient beds, sinks, televisions, light switches, outlets and hand sanitizer dispensers. Then representatives from the full care team of physicians, nurses and parents walked through to share feedback.

"We reviewed bedside tables, tried different sleeper beds, tested the comfort of rocking chairs, examined the distance from the couch to the patient's bed, to the television and to the phone charger built into the wall," Flynn says. "Everyone had a different perspective. For me, the lighting was really important. When my son was in the hospital, I didn't want

PATIENT ROOMS ARE DESIGNED TO BE HAVENS FOR FAMILIES. TWO PEOPLE CAN SLEEP overnight with the patient. Youngsters can play among animal sculptures (below) and spend time in the story corner (right).



# AT A GLANCE

## HIGHLIGHTS OF THE NEW LUCILE PACKARD CHILDREN'S HOSPITAL STANFORD

**NEARLY 15 YEARS IN THE MAKING**, the new Lucile Packard Children's Hospital Stanford more than doubles the size of the existing facility by linking a new main building with the original campus. Here's what you can expect:



### Added features

The new hospital includes more space and other elements throughout the campus, with additions including:

- 521,000 additional square feet of building space designed to be easier to navigate and more open, welcoming and child-friendly.
- 420 parking spaces, including 22 electric vehicle charging stations.
- 149 new patient beds in rooms that have a family focus, bringing the combined hospital bed total to 361.
- Six new surgical suites to give physicians immediate access to imaging and other diagnostic equipment, bringing



the total number of hospital surgical suites to 13.

- 3.5 acres of new garden and green spaces that highlight Northern California's natural environment in plants and play spaces.

### Technological advances

Innovative and advanced medical technologies make the facility more efficient and treatment more effective. They include:

- A neuro-hybrid suite for neurosurgery that combines diagnostic imaging services within the operating room. Neurosurgical patients are traditionally moved from the operating room to intensive

care, then to imaging to determine whether a procedure was successful. But in the hybrid suite, surgeons have ready access to an MRI so they can re-image a patient to ensure a tumor has been completely removed before they finish the surgery. Avoiding multiple steps significantly shortens surgery times, which saves money and means patients spend less time under anesthesia and have shorter hospital stays.

- One of the nation's only stand-alone combined PET/MRI scanners that is dedicated to pediatric patients and measures how their tissues and organs are functioning to understand how diseases are behaving in their bodies. This allows physicians to create a personal treatment plan for every patient. The machine, designed in part by Stanford University engineers, provides less radiation exposure and is smaller and less invasive than equipment used for adults, which makes imaging faster and more comfortable for children.
- A high-intensity focused ultrasound device that pairs ultrasound and MRI technologies to shrink or remove tumors using sound wave blasts. It is used primarily to treat bone tumors, some of which might have required surgery or even amputation in the past. [See *related story*, page 16.]

### Space where kids can be kids

Features are included to help "normalize" children's experiences in the hospital. Additions include:

- Playrooms on each floor for pet therapy, arts and crafts, and other activities that involve the whole family. Playrooms are designated by age group so all patients have age-appropriate activities.

- A wall of large digital, interactive screens and sensors in the lobby. Patients and visitors can select nature-based environments to display on the screen — including a sandy beach or underwater scene. Then they can move their arms around to virtually paint a rainbow in the sky, or swim alongside sea creatures, while their body movements appear on screen. The wall doesn't require them to touch anything, which is important for controlling infection, particularly for patients whose immune systems are compromised.

### Focus on sustainability

The new facility is built to ensure an environment-friendly approach.

- Gardens and green space are irrigated with rainwater, water from condensation extracted from dehumidifying indoor air and wastewater from the hospital's hemodialysis filtration system. These water sources are collected in two 55,000-gallon underground cisterns. This is expected to save 800,000 gallons of water a year.
- Water-conserving dishwashers and sterilizers, on-demand sinks, low-flow bathroom fixtures and the elimination of water-cooled pumps and air compressors are expected to result in an estimated 38 percent drop in water usage compared with a standard hospital.
- A shading system on the exterior of the building reduces solar gain (increase in temperature caused by the sun) and decreases the need for air conditioning.
- A dashboard in the main lobby displays ongoing energy and water usage — making it fun for kids and easy to see how much energy is being used in various areas of the campus.

# ultrasound S O L U T I O N

## A GENTLER WAY TO SHRINK KIDS' TUMORS

She's only 5 years old, but after a summer of swimming lessons, Cadence May has mastered an impressive backstroke. She's got the floating down pat, her mom says. She flutter-kicks with vigor. And she can stretch each arm way up behind her head, dig deep into the water of her neighborhood pool and propel herself smoothly along.

"I didn't realize she would have full extension of her arm," says Annette May, Cadence's mother, recalling the moment she saw her daughter demonstrate her stroke for other students in swim class.

"She could do it flawlessly," May says. "I was proud — and surprised."

Watching Cadence master the backstroke was poignant for good reason: She was born with a desmoid tumor on her right forearm. Although these noncancerous tumors do not spread around the body, desmoids can grow aggressively at the site where they originate, leading to pain and permanent damage. Cadence's tumor threatened to cause atrophy in her muscles and encase blood vessels and nerves, which could have seriously impaired movement of her arm and hand. When her doctor diagnosed the tumor in 2014, treatment options for children were bleak.

But instead of sustaining permanent damage to her arm, this young girl had an unusual opportunity to become a medical pioneer. In an April 2016 procedure at Stanford, when she was 3, Cadence became the youngest child in the world to be treated — for any disease — with a technology called high-intensity focused ultrasound. Today, her tumor isn't completely gone, but it's also not bothering her, and her doctors are using focused ultrasound to keep it that way.

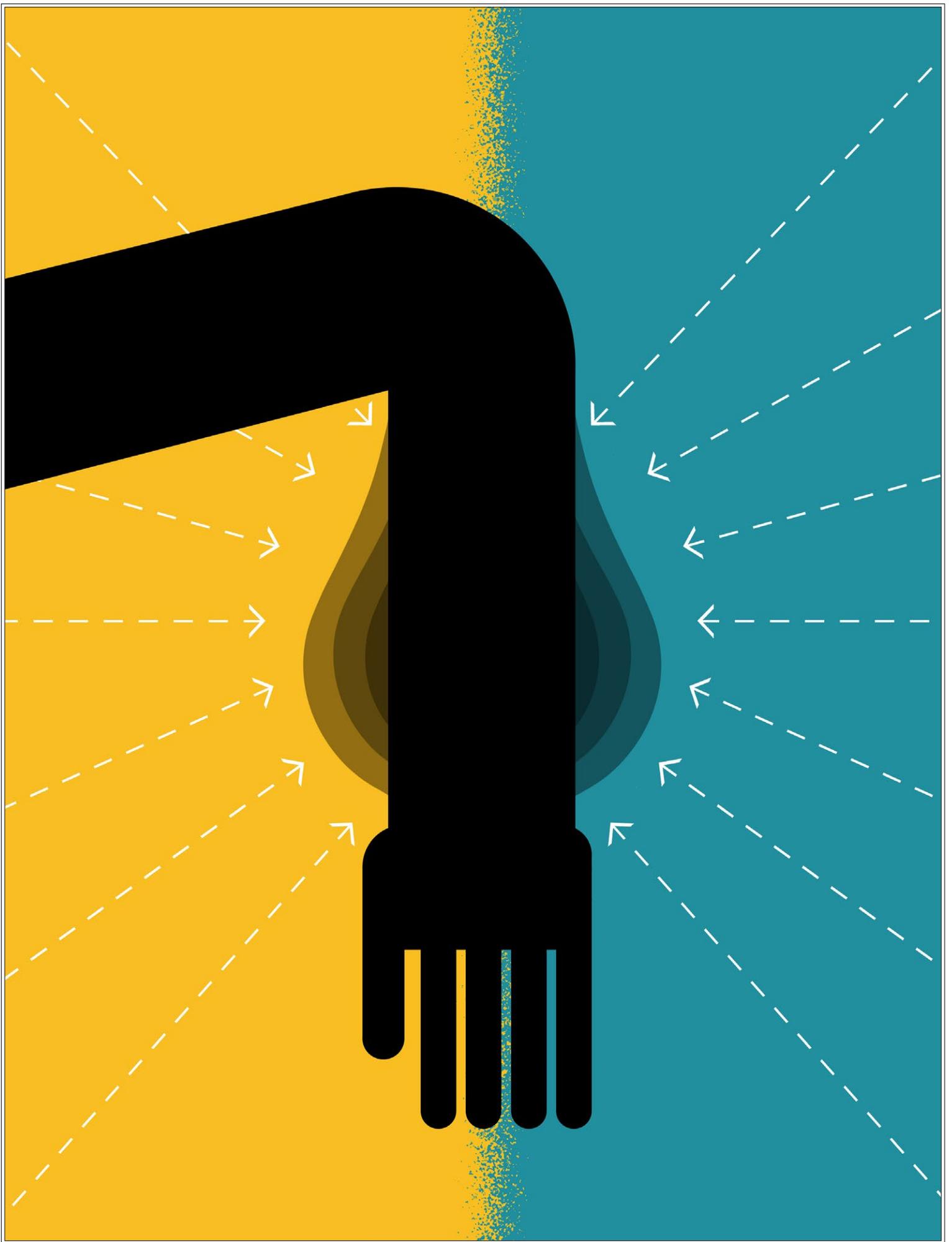
Children with other diseases stand to benefit, too. Though the ultrasound technique helping Cadence has been used to treat a handful of conditions in adults for more than a decade, it's undergoing a renaissance that promises to be especially advantageous for kids.

### FOCUSING THE BEAM

The idea behind focused ultrasound is simple: Instead of projecting high-frequency, impossible-to-hear sound waves diffusely through tissue, as doctors do during ultrasound imaging, they focus the sound waves on a single location to heat and kill only a region of problematic tissue. The waves originate from a transducer, traveling through healthy tissue in a cone shape and cooking only what's located at the tip

BY ERIN DIGITALE

ILLUSTRATION BY TERRY ALLEN



of the cone of energy. The procedure is done in a magnetic resonance imaging scanner to help doctors direct the high dose of energy to just the right spot.

“It’s like taking a magnifying lens to focus sunlight and burn a hole in a leaf,” says Pejman Ghanouni, MD, PhD, assistant professor of radiology at Stanford, who used the technology to treat Cadence. “The tissue at the focus is heated and destroyed. We use MRI to image what we’re going to target, and also to monitor the heating. We try to ensure that the target is adequately heated while avoiding damage to the surrounding tissues.” The ultrasound transducer delivers several zaps of energy, each lasting 20 to 30 seconds, throughout the targeted area. (Some physicians use ultrasound imaging to guide focused ultrasound treatment, but this does not allow monitoring of how much the tissue heats up.)

“It’s completely noninvasive, doesn’t require a knife, and you can reach inside the body and destroy tissue in a region as small as a grain of rice,” says James Geller, MD, a pediatric oncologist at Cincinnati Children’s Hospital who referred Cadence to Stanford. Geller’s team is now launching a focused ultrasound program of its own, one of about half a dozen such programs treating kids across North America.

Focused ultrasound was first approved by the U.S. Food and Drug Administration to treat uterine fibroids; it also has approval for relieving pain from cancerous tumors that spread into bone and treating essential tremor. Nearby tissues are sometimes overheated, with sunburnlike burns or blisters possible if the targeted area is near the skin, though physicians are developing methods for using water cooling to reduce this risk. After the problem area is heated and killed, the body gradually absorbs the dead tissue.

Ghanouni and other experts think the advantages of focused ultrasound justify expanding its uses much further. The technique is especially promising for growths that cause damage in the areas where they appear but don’t spread around the body, such as desmoids, certain bone abnormalities, benign brain tumors and other neurologic defects. For locally aggressive but noncancerous tumors like desmoids, using high-intensity focused ultrasound requires doctors to shift their thinking from permanently vanquishing a tumor to controlling it — but it also offers distinct advantages in terms of speed and safety.

“The idea of being able to put a child in an MRI scanner and have their lump treated when they come out sounds almost 22nd-century,” Geller says.

WHEN CADENCE WAS BORN IN 2012, her parents wondered what was wrong with her arm. “We initially noticed what looked like trauma to her right arm,” says Aaron May, Cadence’s father. “It just looked swollen. We kind of joked that it looked like a Popeye forearm because it was noticeably larger than the other one.”

Physicians in the family’s hometown of Louisville, Kentucky, said the lump would disappear on its own. When it didn’t, the Mays requested a referral to Cincinnati Children’s, where, in June 2014, Geller’s team diagnosed a desmoid tumor. These rare tumors occur in 900 to 1,000 people in all age groups nationwide each year.

“Desmoids are unique because they’re not cancer; people don’t die from them, but people are tortured by them,” says Raffi Avedian, MD, assistant professor of orthopedic surgery at Stanford, who helped treat Cadence.

The tumors infiltrate muscles and cause pain and deformity, he explains, and traditional cancer-fighting techniques often fail. “People get all the side effects of radiation, chemo and surgical scars, and a lot of times the tumor comes back,” Avedian says. “There’s all that effort for really no benefit.”

For Cadence, Geller initially suggested a year of chemotherapy, a then-common approach. Cadence, who had just turned 2, had a port inserted under the skin of her chest to enable weekly intravenous chemo infusions.

Although she didn’t have serious side effects from the drugs, the weekly two-hour drives between Louisville and Cincinnati were draining for the whole May family. And Cadence’s port had to be accessed with a needle inserted through her skin each week, which she hated. She received numbing cream before each treatment, but could still feel the needle. Often, four to six people had to hold her down so her nurse had the best chance of hitting the port on the first try.

“It was pretty painful, watching her scream in pain week after week for 26 weeks,” her mom says. After six months of chemotherapy, the desmoid had grown slightly. Feeling discouraged, Cadence’s parents ended the infusions. Ten days of oral chemotherapy — with the side effect of a rash so severe it landed her in the ICU — was equally disheartening, so the family stopped Cadence’s treatment completely. She continued receiving MRI scans for monitoring; in early

Focused ultrasound is especially promising for treating growths that cause damage in the areas where they appear but don’t spread around the body.

2016, after nine months without medication, the tumor had grown more. That's when Geller referred the Mays to Stanford, where Ghanouni's team offered to treat Cadence. The Stanford physicians had been studying focused ultrasound for other diseases and had recently gained permission to offer it to desmoid patients on a compassionate-use basis.

### AVOIDING OVERKILL

**H**EARING ABOUT FOCUSED ULTRASOUND gave the Mays their first real hope. "It was less invasive, it wasn't going to be painful and she wasn't going to have to be cut open," Aaron May says. The couple had already heard that surgery was a poor option.

"Even after resections where the pathologist reports that the margins are clean, there's still a 50 percent chance that a desmoid will come back," Ghanouni says. "Our surgeons aren't excited about operating on these tumors."

If focused ultrasound hadn't existed, Stanford's team could have offered Cadence surgery, albeit with large risks. "The expected side effects would have been related to removing muscles and nerves, leaving her with significant functional loss of her arm," says Avedian. That would have been the best-case outcome: Before focused ultrasound was introduced, Avedian sometimes had to amputate limbs of children who had aggressive returning desmoids.

Radiation, which is a good option for many adults with desmoids, is less likely to resolve pediatric desmoids and carries higher risks for kids. "If you expose a child to radiation, you also give them a 1-in-20 chance in their lifetime of developing an actual sarcoma, a malignant tumor," Ghanouni says. For an older adult, in whom the radiation is more likely to be effective, that 1-in-20 risk may seem more acceptable.

"But the risk-to-benefit relationship is very different in children," Ghanouni says, noting that kids also have many decades of remaining life expectancy in which a secondary cancer caused by radiation could appear. "Kids are not small adults, so we really need different treatment options."

### 'NERVE-WRACKING' PROCEDURE

**S**HORTLY AFTER 8 A.M. ON April 14, 2016, Cadence was put under general anesthesia at Lucile Packard Children's Hospital Stanford, then wheeled to Stanford Hospital and positioned on the MR-guided focused ultrasound table. Although the focused ultrasound equipment is located at Stanford's adult hospital, a pediatric anesthesia team from Packard Children's collaborated with Ghanouni throughout the

procedure to keep Cadence safe. (Packard Children's new hospital, opening in December, will have focused ultrasound equipment dedicated to pediatric patients.)

"It was nerve-wracking treating someone so young," Ghanouni says. The technology had been used for a few desmoid tumors in adults, and Ghanouni and Avedian had collaborated on five desmoid cases in teenagers, making them the first U.S. physicians to use it to treat pediatric patients.

In Cadence's case, the team's main concern was to protect her skin, nerves and bone. Ghanouni planned to limit the ultrasound treatment to the tumor's core, aiming to kill 30 percent of it. When Avedian met with the Mays, he used MRI images to show where the high-energy beams would go.

"We were taken aback a little," Aaron May says, recalling when the couple first heard the plan. They had hoped physicians could eradicate all of Cadence's tumor, yet understood the need for caution.

During the procedure, Ghanouni and his colleagues spent nine hours zapping the middle of the lump bit by bit. At the end, they were confident the tumor's core was dead. "He did what he said he was going to do, and he told us this is not a one-time treatment, that he could go a little further each time," May says. Indeed, a major advantage of focused ultrasound is that, unlike toxic chemotherapy or DNA-altering radiation, there is no limit to the number of treatments a patient can receive.

Cadence stayed overnight at Packard Children's for monitoring as the anesthesia wore off, and was her usual self soon after. "The very next day, she was playing on the playground like nothing had ever happened," Annette May says. That day Cadence had no trouble swinging from the monkey bars using both arms, her mom says.

Seeing how quickly Cadence bounced back increased the confidence Ghanouni and Avedian had in what they were doing. "What we're learning from desmoids can translate to sarcomas and other tumors as well," Ghanouni says.

### TREATING OTHER TUMORS

**A**VEDIAN, GHANOUNI AND THEIR Stanford colleagues are continuing to study how focused ultrasound could be used against several types of tumor. They have conducted a clinical trial for patients with malignant sarcomas — cancerous soft-tissue and bone tumors — and have used focused ultrasound to treat benign bone tumors called osteoid osteomas, as well as vascular malformations, which are overgrowths of blood vessels. For all of

C O N T I N U E S O N P A G E 47

# no place to call

## H O M E

HOUSING INSECURITY PUTS CHILDREN'S CARE,  
TREATMENT AT RISK

# U

ntil a few months ago,

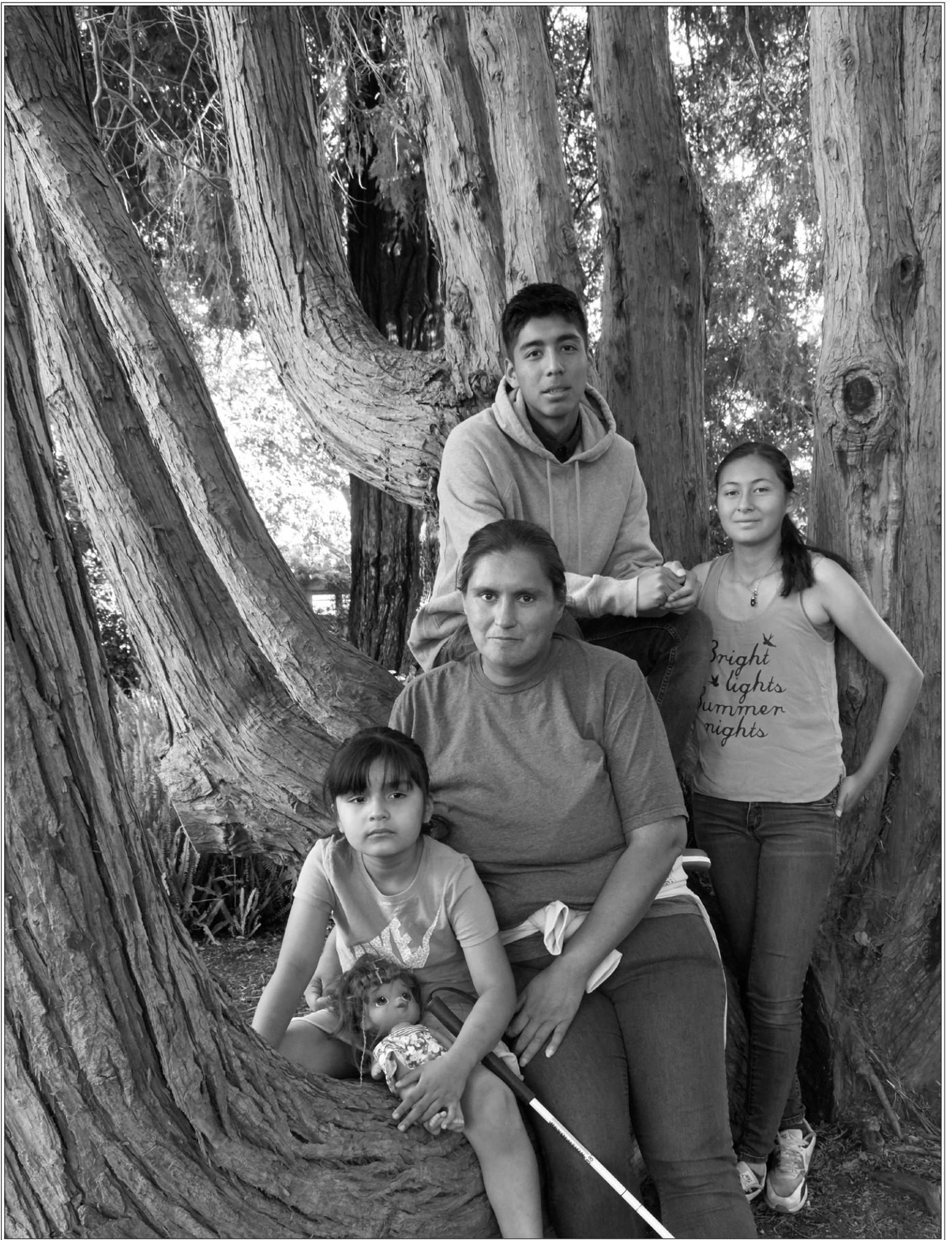
"home" meant one thing to 5-year-old Joy Gutierrez: A two-bedroom apartment in Daly City, California, shared with her mom, two siblings, her favorite aunt and four cousins. It wasn't fancy, but Joy — born with a genetic disease that causes blindness — loved it. She knew the voices of everyone in her family, how to move through the familiar space and how to turn on the TV for episodes of *Dora the Explorer*. Joy's mom, Patricia Gutierrez, walked her to preschool, the local playground and a nearby mall. "She likes to be independent," Gutierrez says of Joy, who was beginning to learn her Braille letters in preschool and was becoming adept at using a white cane to navigate the shadowy world apparent through her extremely limited vision. "If it's hard, she wants to try."

But in June, Gutierrez and her sister received an eviction notice on their shared apartment. By early August, unable to find housing she could afford, Gutierrez and her children were living in a shelter 12 miles from their old neighborhood. Joy misses their apartment, their neighborhood, and her aunt and cousins. She keeps asking why they can't move home. "She wants to go back," Gutierrez says. "It's been very hard."

BY ERIN DIGITALE

PHOTOGRAPHY BY LESLIE WILLIAMSON

Patricia Gutierrez and her children, Joy, 5, Carlos, 17, and Rosa, 14, are looking for housing after being evicted from their Daly City apartment.



Harder still is the fact that Gutierrez is unsure she'll be able to remain in the Bay Area. San Francisco is home: She grew up there before the current era of vertiginous housing costs. Since Joy was born in 2011, Bay Area rents have risen more than 25 percent, to median levels of nearly \$2,800 per month in Silicon Valley and \$3,900 per month in San Francisco. Home prices have jumped 75 percent, to a median sale price of more than \$1.2 million for San Francisco and San Mateo counties and \$755,000 across the Bay Area. Gutierrez is a single mom with three kids, two of whom are disabled. She sustains her family with child support, disability payments and various types of public assistance. For families like hers, the region is increasingly unaffordable.

To help families in similar situations, several Stanford pediatricians are working to strengthen the options for doctors and families tackling social problems that can have damaging downstream effects on children's health. Yet the collision be-

ment associated with many health problems. After genetic and neurological testing, Alcorn and her colleagues arrived at a devastating diagnosis: Leber Congenital Amaurosis, a genetic disease that interferes with the function of the retina.

"It's a very severe form of childhood blindness," Alcorn says. The disease affects about 1 in 50,000 to 80,000 children and can be caused by mutations in any of at least 17 genes. The disease is transmitted through a defective gene copy from each parent. Most parents don't know they carry a disease-causing gene until their child is diagnosed.

Alcorn discussed the disease with Gutierrez: Joy would probably have normal intelligence and learning capabilities, but would be severely visually impaired, likely legally blind. She might poke at her eyes to produce stimulus to the retina, and Gutierrez should try to discourage this. Gutierrez would need to help Joy navigate their home and neighborhood, and

## 'EVICTION IS STRESSFUL FOR families even WITH A CHILD WHO DOESN'T HAVE

tween housing and health creates problems that are extraordinarily hard to solve.

Case in point: If Gutierrez moves away, it means pulling her children from the support network she's fought to develop for them. Her son, 17-year-old Carlos, has no special medical needs, but it's his senior year in high school, a wrenching time to leave. For the girls, it's even harder: 14-year-old Rosa, who has significant developmental disabilities, uses a local nonprofit organization that helps developmentally disabled people become more independent, and Joy has been seen since infancy by Deborah Alcorn, MD, Service Chief, Pediatric Ophthalmology at Lucile Packard Children's Hospital Stanford.

"I don't want to move far because I love Dr. Alcorn," Gutierrez says. "She's been helping my daughter ever since she was a baby."

### A DEVASTATING DIAGNOSIS

J OY WAS A FEW WEEKS OLD WHEN GUTIERREZ NOTICED HER DAUGHTER'S erratic eye movements. Joy's pediatrician referred her to Packard Children's, where, at the age of 7 weeks, the little girl was seen by Alcorn, who is an associate professor of ophthalmology and of pediatrics at the Stanford School of Medicine.

Alcorn noted that Joy had nystagmus, a roving eye move-

advocate for what Joy needed at school. Given Joy's severe early visual loss, Gutierrez needed to know that other areas of Joy's development, especially social development, could also be delayed.

"Some parents get a dismal diagnosis, and they assume 'There's nothing I can do,'" Alcorn says. "Not this mother: She told me right away, 'I want to know what resources I have available, and I want to make sure I get all of them.'"

Alcorn referred Joy to the Blind Babies Foundation, which sent an expert to the family's Daly City apartment. At the age when most babies would start getting into everything, Joy lay still. "I guess she was scared," Gutierrez says. "They really helped support me, getting her active and making sure she'd be able to move around and do stuff like normal kids."

As Joy entered preschool, Alcorn contributed to Joy's Individualized Education Program, specifying that she needed comprehensive visual services, including Braille instruction and, eventually, help using a white cane.

Today, Joy has minimal vision; at best, she can tell if a hand held near her face is moving or stops. Highly sensitive to light, she often wears sunglasses. Some days her vision is a little better, sometimes worse. Alcorn continues to monitor her.

Alcorn also tries to instill the right amount of hope. Some LCA patients are receiving gene therapy, a treatment that

doesn't produce normal vision but makes daily life easier, she has told Gutierrez. Gene therapy is not yet available for the genetic defect Joy has, but that may change. Alcorn wants Joy to continue being seen at Packard Children's because an academic medical center is a superb place for a child with a rare genetic disease to access such cutting-edge treatments.

#### NEED FOR ADVOCACY

**A**LCORN WAS ASKING A ROUTINE QUESTION ABOUT THE FAMILY'S home life during Joy's most recent appointment in June when she learned the painful news that they were being evicted from their Daly City apartment.

"Joy was very upset," Alcorn says. "She was very attached to her aunt, and now her aunt was not going to be able to live with them."

## A medical issue!

Ideally, when the stability of a family's life is threatened, pediatricians can provide a bridge to resources that help.

"People may be worried about using services in the community, but they come to us," says Dana Weintraub, MD, clinical associate professor of pediatrics at the School of Medicine and an advocate for families in need. "We're a place of trust."

Many pediatric hospitals and health care systems employ social workers as front-line caregivers to address families' non-medical needs. Packard Children's has about 40 full-time social workers, several of whom specialize in children with specific medical problems, such as cancer or organ transplantation. Social workers often link families to other sources of help — including nonprofit or advocacy organizations.

By the time she saw Alcorn in June, Gutierrez had already been connected to the Legal Aid Society of San Mateo County via her social worker at California Children's Services, which provides case management to children with certain severe medical conditions, including blindness. Gutierrez had sought legal aid for assistance with Joy's Individualized Education Program, which she felt her daughter's preschool was not following. Soon her attorney was also asking about her eviction.

The household had kept up with its \$2,000 monthly rent payments, but the landlord was fed up with the family's requests that he repair the toilet, which kept flooding their unit, Gutierrez

says. In Daly City and many other Bay Area jurisdictions, landlords can evict tenants without cause. The landlord gave 60 days' notice, as required, leaving the family in a difficult situation. The family's requests for repairs weren't in writing, making it hard to prove the landlord was retaliating against them.

"We gave them lots of advice and support, but they decided they didn't feel like they could defend against an eviction," says Kate Stanford, JD, the Legal Aid Society of San Mateo County attorney who has been working with the family. Many families won't complain about habitability issues, she says, because they fear exactly what happened to Gutierrez: Ask for reasonable repairs, get served with an eviction notice. "And once a family is homeless, there's not a lot to be done legally," Stanford says. "We shift our focus to making sure the family has the income supports — food stamps and other public benefits — to become stable again."

When the eviction date arrived and Gutierrez had not secured housing, the county put her and her children up in a hotel for a few days, then offered the spot in the shelter.

"Eviction is stressful for families even with a child who doesn't have a medical issue," says Weintraub. "But when a child with complicated health care needs is evicted to the street or a shelter, they're not getting the care they need in a safe environment."



Dana Weintraub, MD, is a clinical assistant professor of pediatrics at the School of Medicine and an advocate for families in need.

For Joy, any change of environment increases her risk of injury as well as her sense of disorientation. Although she's an active kid — who, with help, adores using playground slides and swings — it's difficult for her to navigate the shelter, where the family has a small bedroom to themselves but must use a large, shared kitchen and living areas that are not laid out with a blind child in mind. "I'm with her most of the time, watching for her. She will bump into stuff and trip and fall," Gutierrez says. Joy and her siblings are entitled to remain in their schools in Daly City, and are now being bused 30 minutes each way.

Beyond helping individual families, physicians also have opportunities to shape policy at a larger scale in their communities, as politicians and other influencers see them as trustworthy sources of expertise on vulnerable kids, says Weintraub.

"So much of what impacts children's health is local," says Lisa Chamberlain, MD, associate professor of pediatrics. Over the past 15 years, Chamberlain, Weintraub and their colleagues have secured many local advances for children's health: Packard Children's provided financial support when Santa Clara County became the first in California to create a low-cost health insurance program that covered all children residing in the county, regardless of their legal immigration status, for instance. (The hospital also supported similar programs in nearby San Mateo and Santa Cruz counties, and supported the development of a state bill that in 2016 extended eligibility for this type of health coverage to all children residing in California.) Packard Children's played a large role in providing logistical support, funding and coordination with local and federal officials to establish and maintain the Ravenswood Family Health Center, an East Palo Alto clinic that provides free or low-cost medical care to needy patients near Stanford. And, in 2012, Chamberlain worked with a local school district to start a summer lunch program for children who receive free lunches during the school year.

Chamberlain, who has been medical director of Stanford's Pediatric Advocacy Program since 2000, was recently named associate chair of policy and community engagement for the School of Medicine's Department of Pediatrics. In that role, she is developing a strategic community engagement plan that recognizes and strengthens long-established partnerships between Stanford and other community caregivers looking out for at-risk families.

Yet, Chamberlain worries that the financial engine of Silicon Valley is leaving a lot of families behind. "Because of our economy, we're facing really significant risks right now," she says. There's more food insecurity as families shift their incomes to meet rising rents, many extended families are crowded into small apartments, and parents often face very

## 'BECAUSE OF OUR ECONOMY,

long commutes to reach their jobs. All of these elements of the housing crisis can hurt kids' health.

The broader outlook is important to doctors on the ground, Alcorn says. "You don't just take care of the child; you kind of inherit the whole family," she says. "I want to do more than just ophthalmology for kids. It's not like I'm just coming in, checking their eyes and they're out the door."

### PREVENTIVE LAWYERING

**W**HEN WEINTRAUB CAME TO STANFORD FOR FELLOWSHIP training in 2002, she joined an American Academy of Pediatrics physician advocacy group, which soon hosted a guest speaker from the country's first pediatric medical-legal partnership, located in Boston. Through these partnerships, pediatricians screen patients for legal problems and connect families to pro bono or low-cost attorneys who can head off health crises.

"It resonated with me because of my work with families dealing with poverty," Weintraub says. "They were struggling with issues that we as pediatricians aren't trained to address, but legal professionals are able to handle."

After receiving support from the hospital's leaders, Weintraub in 2004 founded the Peninsula Family Advocacy Program, a collaboration between Packard Children's and the Legal Aid Society of San Mateo County. (Kate Stanford, the attorney assisting with Joy's Individualized Education Program, is the partnership's legal director.) Housing challenges were among the first legal problems the team addressed.

"One of our very first cases was a child who was 10 months old, who had been in the ER twice in the past month, once resulting in hospitalization," Weintraub says. The family's apartment was beset with mold, cockroaches and grimy carpeting. A letter from the child's physician to the landlord explaining that these allergens appeared to be fueling the child's asthma — and mentioning the housing habitability codes that were possibly being violated — got a rapid response. The landlord let the family stay rent-free in another unit while the carpet was removed and the cockroaches exterminated.

"After that, the child's breathing improved," Weintraub says.

# we're facing REALLY SIGNIFICANT risks RIGHT NOW'

The landlord's quick action made an impression on Weintraub. Coming from a doctor, the message that a housing issue could be harming a tenant's health carried a lot of weight.

In addition to housing, the partnership addresses many other social and legal problems, including immigration issues, domestic violence, special education, or being unable to pay bills or buy food. But families still fall through the system's cracks. Once a family has been evicted, they are, to a large extent, at the mercy of the housing market, and there is little that pediatricians — or anyone else — can do.

## FEW TENANT PROTECTIONS

**A**S BAY AREA RENTS RISE, the reasons behind local evictions are evolving, says Shirley Gibson, JD, directing attorney of the HomeSavers Project, run by the Legal Aid Society of San Mateo County. The project, founded in 2007, provides free assistance to families struggling to keep their housing.

Ten years ago, nonpayment of rent far outstripped other reasons for local evictions; today, no-cause evictions are equally common, a sign of a housing market that heavily favors landlords.

"We don't get a lot of candid information from landlords, but we have enough anecdotes to suggest that, hey, they cleared out that whole building of families with kids to attract tech workers who work down the street," Gibson says. In most housing markets, getting rid of all your tenants would be "cuckoo," she adds. "Why would you do that, except if you can double the rent?"

Racial and ethnic minorities and children are being especially hard hit, according to HomeSavers Project data. Seventy percent of the project's clients who fought evictions between 2012 and 2015 were from households with children, and Hispanic and African-American households are being displaced at rates far above their representation in the county population.

Very few Bay Area communities have tenant protections such as just-cause eviction or rent control. Given the intensity of the region's housing crisis, "the notion that you can just kind of ride out whatever is happening with the housing market and let the market correct itself is not a workable approach," Gibson says.

Building more market-rate housing won't alleviate the

crisis for low-income families, either. "We need to build affordable housing and be precise about what we mean by 'affordable,'" she says.

In other words, will it be accessible to families like Joy's? Few local municipalities have laws to allocate any development funds toward affordable housing, but in those that do, Gibson and other Legal Aid attorneys have brought lawsuits to ensure the laws are followed. Other local agencies, such as the Housing Leadership Council of San Mateo County, advocate with public officials and other decision-makers for more affordable housing.

At press time, Gutierrez still did not know where the family would go when her time allowed in the shelter expires. In mid-October, she estimated that over the previous month, she had inquired about 40 apartments; four landlords replied. All rejected her applications: Her income was too low, they wanted tenants whose income came from jobs rather than public assistance, her credit wasn't good enough, or their units would not accommodate four people, they told her.

Gutierrez has worked in the past, but even with child care help from her sister, Joy and Rosa did not do well. Rosa would go all day without eating or showering. "She'd just lay in bed talking to herself," Gutierrez says. Joy would fall and get hurt. Others lack the patience Gutierrez has for her kids. "I don't get frustrated; I don't push my kids to the side," she says. "They need my attention. I'm fully right there. Joy, all she wants is for me to hug her."

For now, Gutierrez is trying to limit her housing search to Daly City, South San Francisco and San Francisco to enable Carlos to finish his senior year. "Once he's done, I could go anywhere I need to go," she says. Though she's reluctant to move Rosa away from her support system and her friends, and worries about disrupting Joy's medical care, she knows she might have to.

Most of all, Gutierrez longs for stability. She wants to live where "we won't have to move around so much or worry about where we end up afterwards; somewhere where my kids could say, 'This is our home. My mom could pay for it.'" **SM**

— Contact Erin Digitale at [digitale@stanford.edu](mailto:digitale@stanford.edu)

### WEB EXTRAS

See our video at  
<http://stan.md/2zWuhq2>

# SAVING children

Save the Children International was founded by an English woman, Eglantyne Jebb, after World War I to feed starving children. The iconic nongovernmental organization has since grown into a global force at the forefront of efforts to protect children's rights.

Whether responding to humanitarian emergencies, advocating for quality education, intervening when children are most vulnerable — in war, natural disasters or extreme poverty — Save the Children receives worldwide recognition as one of the chief protectors and defenders of children in crisis.

Helle Thorning-Schmidt, the organization's international chief executive officer, is no stranger to diplomacy, advocacy and the global stage. She was Denmark's first female prime minister and led the nation through the global financial crisis in 2007. She joined Save the Children in 2016.

At an international summit this summer in Dubai, United Arab Emirates, Thorning-Schmidt told the audience that it is a priority to help children in a world of abundant harm where violence impacts 15 million of them. "To my organization, Save the Children, there is nothing more urgent than protecting children in armed conflict," she said.

Thorning-Schmidt and Executive Editor Paul Costello communicated by email after she returned to London from the opening of the United Nations General Assembly in New York.

**COSTELLO:** Is this a better world for children or a more threatening world?

**THORNING-SCHMIDT:** The world is facing the worst humanitarian crisis since the Second World War. Conflict and drought have fueled a crisis, leaving 20 million people in Somalia, South Sudan, Yemen and northeast Nigeria in urgent need of food and water. Millions more children are growing up in war zones in places like Syria, South Sudan and Yemen. In Yemen, cholera is infecting a child every minute. This is a disease that should have been consigned to the history books. And millions of children have fled their homes as refugees

and are now living in limbo without basic supplies or an education. We're also seeing a new crisis unfold in Bangladesh, where more than a quarter of a million Rohingya children have crossed the border from Myanmar.

This is a crisis on a scale the world has not seen in a long time, and we need powerful action to help those in urgent humanitarian need. But while it is easy to feel pessimistic when hearing about these crises, the good news is that great progress has been made for children over past decades. Children today are healthier, wealthier and better-educated than ever before. We have made great progress, but there is still a long way to go.

**COSTELLO:** What are the specific dangers that children face when they are displaced and living in refugee camps?

**THORNING-SCHMIDT:** Half of all refugees are children. They have had to flee their homes and many then find themselves living in poor conditions without the right food, shelter and health care.

As well as making sure children have access to the basic supplies they need to be healthy, we need to make sure that they don't miss out on an education.

Half of all refugee children are out of school and this leaves them open to exploitation, radicalization and trafficking. Being in school and learning means these children are safe from dangers like this.

We asked more than 8,000 refugee children and their families what they wanted, and 90 percent of them prioritized education. One day, when peace comes, I hope that the children who have had to flee war-torn countries can return and rebuild their countries. To rebuild their countries, child refugees will need to grow up to become engineers, architects, doctors and business people.

**COSTELLO:** Save the Children recently published a report that looked at the mental health impact of the war in Syria on children. What are some of the major points?

**THORNING-SCHMIDT:** We conducted the largest study ever undertaken of children’s mental health inside Syria during the war. We spoke to 450 children and their parents in places that were besieged, like Aleppo, Damascus, Homs and Idlib. What we found is disturbing — the war is clearly causing deep psychological trauma for the children



of Syria. These children have seen and experienced things that no child should ever face. We heard of children wetting the bed, having nightmares, losing the ability to speak and even becoming suicidal.

Experts say that many of these symptoms are in line with “toxic stress,” which is the most dangerous form of stress response a child can experience and can have a lifelong impact on children’s mental and physical health. But a quarter of children interviewed said they had nowhere to turn. Support services in Syria have collapsed, with hospitals bombed and many doctors and professionals having fled the country.

Without the right help, this trauma could affect their future development. But with early interventions, children can recover from traumatic experiences like these. Save the Children is already working to help these children. For instance, we run child-friendly spaces, protected environments for children to learn and play and where they can get psychological support. Education is also an important part of the solution, and we are providing education for Syrian refugee children.

**COSTELLO:** How critical is national leadership in solving these seemingly intractable problems?

**THORNING-SCHMIDT:** Strong leadership from world leaders and institutions like the United Nations is vital.

It is only because of leadership like this that we have progress. Take child mortality. The number of children dying before their fifth birthday is less than half of what it was two decades ago, and millions of children are alive today as a result. Much of that progress was made in China. China’s leaders made a huge effort to reduce the under-5 mortality rate, and it was largely because of that progress that the world met its millennium target on this. Without that kind of leadership there and in other countries, children would be worse off.

And the contribution that many developed countries make in the form of overseas development assistance has also saved the lives of millions of children. I hope that countries around the world continue to be generous like this. A little can go very far, and investing in international development allows governments to help the most vulnerable people in the world while also serving their own people by helping to create a more secure and stable world.

**COSTELLO:** A significant crisis in many developing nations is lack of access to clean water. What is the impact on children?

**THORNING-SCHMIDT:** Every child has the right to clean drinking water and the nutritious diet they need to thrive. Far too many children do not have access to this basic human need, and this is a leading cause of death in children under 5 because of the diseases spread by unsafe drinking water. Every year, 650,000 young children die of diarrhea. Children should not be dying of diseases like this that we can easily prevent. A big part of our work involves working with governments and communities to improve access to proper sanitation and clean drinking water.

I recently visited rural Kenya, where the worst drought in a decade has left many children severely dehydrated and malnourished. Save the Children is running mobile health clinics and delivering emergency supplies to help these children, but in the long term we need to build better infrastructure so that remote communities are not left without clean water when drought hits.

**COSTELLO:** You travel around the globe and are witness to some of the worst harm inflicted on kids. What gives you the greatest hope?

**THORNING-SCHMIDT:** Children give me hope. I meet children who have been through the most unimaginable hardship yet are still full of hope. Children who had to flee war zones and leave their families and belongings behind, street children who live on their own and don’t even have a name and mothers who can’t afford to feed their babies for days. No matter the suffering, they have endured, they still have hope that things will get better. At Save the Children we are working in 120 countries to make sure that hope becomes a reality for children and things do get better. It is the job of all of us to make sure the world does not let these children down again. **SM**

H I D E

A N D

S E E K

PIONEERING IMMUNOTHERAPY TO FIND AND KILL  
ELUSIVE CANCER CELLS IN CHILDREN

Pediatric cancer specialist Kara Davis was nervous. It was a spring morning in April and she was headed into the hospital to see 11-year-old Salvador De Leon. Sal had leukemia, and he wasn't doing well. After three grueling years of therapy, his most recent relapse left only one course of action: an experimental treatment to seek out and destroy the cancer cells that had eluded conventional cancer treatments. Davis knew that this approach could either cure him or kill him. The treatment, known as CAR-T cell therapy, relies on the use of a patient's own genetically modified immune cells to track down and attack the leukemia cells. Although some children with leukemia like Sal's have experienced stunning, years-long remissions after the therapy, about 30 percent of CAR-T cell recipients experience a temporary but potentially deadly side effect known as cytokine release syndrome.

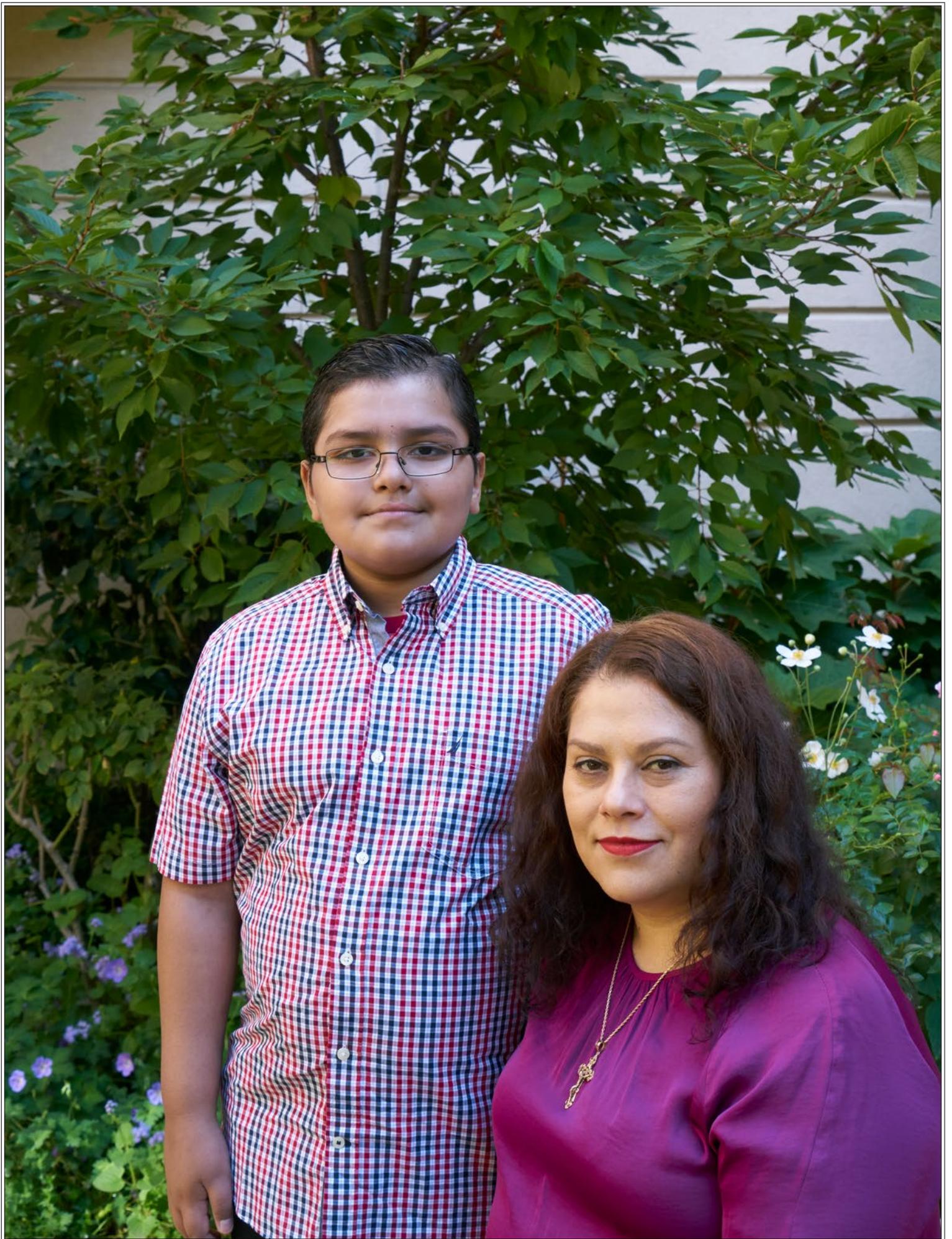
Davis, OD, an assistant professor of pediatrics at the Stanford School of Medicine, was concerned because Sal had reacted poorly to previous rounds of chemotherapy. Did this mean he was likely to struggle with the CAR-T therapy as well?

"I was very worried," Davis recalls. "But there really weren't any other good options for Sal."

BY KRISTA CONGER

PHOTOGRAPHY BY LESLIE WILLIAMSON

Salvador De Leon and his mother, Maria De La Cruz



When she broached the subject of the new treatment with Sal's family, his mother, Maria De La Cruz, didn't hesitate. "If it has any chance of saving his life, we will do it," she recalls saying. "We will do whatever it takes."

CAR-T cell therapy is a new form of what's known as cancer immunotherapy, and it's been uncommonly successful. So successful, in fact, that in August the Food and Drug Administration fast-tracked its approval of a CAR-T cell treatment for children like Sal with relapsed or unresponsive acute lymphoblastic leukemia. Marketed by Novartis, it's the first cell-based gene therapy approved by the FDA for use in humans.

It's also big money. In the same week of the FDA approval, the pharmaceutical giant Gilead Sciences purchased Kite Pharma for nearly \$12 billion to gain control of its version of the CAR-T cell therapy. It seems the move paid off. In October, the FDA approved the Kite-developed therapy for treatment of adults with certain types of lymphoma.

Currently the CAR-T cell therapy must be custom-made for each patient, and is estimated to cost about \$475,000 per child. But the results have been astounding. Some desperately ill children have been seemingly cured of their cancer with just one treatment.

"This is without a doubt a watershed moment in the history of cancer therapy," says Stanford's Crystal Mackall, MD, a cancer immunotherapy expert and former head of the National Cancer Institute's pediatric oncology branch.

But the treatment isn't perfect. It kills healthy B cells as well as their cancerous peers, which compromises a patient's immune system. It's unknown exactly how long the genetically engineered cells stay in the body — or even how long they should stay. It's unbelievably expensive (one watchdog group claims it's on track to be the most expensive drug ever marketed). And it so far has been relatively ineffective against solid tumors.

Now researchers at Stanford, including Mackall, Davis and their colleagues, are investigating ways to make CAR-T cell therapy faster, cheaper, safer and more broadly applicable to other types of cancers. They're experimenting with combination therapies that target more than one molecule on the leukemia cells. They're also looking for new targets on cells in solid tumors, and brainstorming ways to reduce the cost. And, of course, they're closely following the progress of the kids like Sal in ongoing clinical trials at Stanford.

Although they are quick to point out the potential caveats of the CAR-T cell treatment, it's hard not to be moved by the excitement in their voices. "Prior to CAR-T cell therapy, you would not even use that word, 'cure,'" says Davis. "Instead I'd suggest other treatment options that might give the family a bit more time together."

Ronald Levy, MD, a pioneer in the field, concurs.

"I've been working in the field of cancer immunotherapy for 40 years, and there's never been a more exciting time," says Levy, who is the Robert K. and Helen K. Summy Professor at Stanford. "Some of the responses we're seeing with this treatment are nothing short of miraculous. The world of cancer immunotherapy has changed forever."

On that April morning, Davis, a mother of two children about Sal's age, was desperately hoping to change Sal's world. As his modified T cells were infused through an IV in his arm, Sal's care team monitored him for any negative reaction.

"But he just breezed through," says Davis. "He did so well, in fact, that I began to worry about the other possibility: that maybe the cells just weren't working. So we all just held our breath for the next month."

**S**AL'S JOURNEY BEGAN IN THE SPRING OF 2014, WHEN HE WAS 8 YEARS OLD. The inveterate Oakland A's fan and video game lover had been struggling with what seemed to be allergies and was having trouble sleeping. Eventually, De La Cruz began to suspect there was something more seriously wrong.

"He was really tired, so I decided to take him to see the doctor," she recalls. "The next thing I knew, the doctor was asking me if I knew what leukemia was."

About 10,000 children age 14 and younger are diagnosed with cancer each year in the United States; acute lymphoblastic leukemia, or ALL, accounts for about a third of the total. Fortunately, it is one of the most treatable pediatric cancers. Ninety percent or more of children with the disease respond well to chemotherapy and quickly achieve remission. Many are cured completely. But the situation is much more dire for those who either don't respond to treatment, or whose cancer recurs. About 30 to 50 percent of these children die within five years. These statistics, coupled with the prevalence of the disease, place ALL on the top of the heap of deadly cancers in children even though most patients are cured.

Unfortunately, Sal's cancer cells harbored a dangerous swap between the DNA at the tip of chromosome 22 and the tip of chromosome 9, creating a hybrid known as a Philadelphia chromosome. The swap married portions of two important genes — leaving one, an important regulator of cellular growth, permanently stuck in the "on" position. Relatively rare in children with ALL, the presence of the Philadelphia chromosome leaves patients less able to achieve remission with standard chemotherapy and subject to quick relapse if

remission is achieved. Five-year survival rates of these relapsed patients are only about 10 percent.

“This situation is very difficult to treat,” says pediatric oncologist Catherine Aftandilian, MD. “For these kids to have their best shot, we have to give very intense chemotherapy. Nearly all these patients end up in the intensive care unit as a result of the treatment.”

Genetic missteps like the Philadelphia chromosome are one reason children’s tumors tend to be better than adults’ at hiding out in normal tissue, escaping the hordes of immune cells that patrol our bodies looking for trouble. That’s because kids’ cancer cells have had less time to accumulate the many genetic mutations that build up over the course of a lifetime of cigarette puffs or regular exposure to ultraviolet rays. Each of those changes stands a chance of creating a new target upon which the immune system can pounce.

Instead, cancer cells in children often arise as a result of one or two powerful mutations. These alone are sufficient to send a cell spinning off the normal developmental track and into out-of-control cell division. But these lone-wolf mutations don’t always create the types of red flags our immune system is looking for.

“In many ways childhood cancers are the most elemental forms of cancer,” says Mackall, who is a professor of pediatrics and of medicine, as well as associate director of the Stanford Cancer Institute and director of the Stanford Center for Cancer Cell Therapy. She also leads the Stanford-based center of the Parker Institute for Cancer Immunotherapy.

“A child’s cells, which have tons of development and expansion potential, can go from being healthy to full-bore cancer seemingly overnight. And these cancers tend to grow quickly and aggressively. But, because these cancer cells are genetically more similar in terms of mutations to normal developing tissue than adult cancer cells are, it is harder for the immune system to recognize them as dangerous.”

As a result, even some very promising immunotherapies in adults have been relatively unsuccessful in children. It’s no good trying to amp up a nonexistent immune response, for example. Instead it has been necessary to craft a whole new approach.

**I**RONICALLY, THE ROOTS OF CANCER IMMUNOTHERAPY ARE AS OLD AS THE PYRAMIDS. The ancient Egyptians recognized a relationship between bacterial infection and cancer, and even deliberately cultivated infections in tumors in the hopes of causing regression of the mass. Throughout the centuries, doctors have attempted to fight fire with fire, balancing the risk of deadly

‘A child’s cells, which have tons of development and expansion potential, can go from being healthy to full-bore cancer seemingly overnight. And these cancers tend to grow quickly and aggressively.’

infection with the near-certain death from cancer.

William Coley, MD, a physician at New York City’s Hospital for Special Surgery in the late 1800s, was one of them. After losing a patient to what was probably a rapidly spreading sarcoma, and noting that others battling an unrelated infection survived, he devised a concoction of bacteria he hoped would provoke a cancer-fighting immune response. He began marketing the injectable treatment as “Coley’s toxins” in 1899, and these toxins continued to be used intermittently through the mid-1900s as a modestly successful treatment for some types of cancers.

Over the next decades, though, the concept of immunotherapy began to fall out of favor as radiation

and chemotherapy became more prevalent. And a growing understanding of the immune system and its need to distinguish “self” vs. “non-self” during development made it seem unlikely that the body would have the wherewithal to kill off tumors arising from its own tissue. A few researchers, however, continued to argue for the concept of “immune surveillance,” which suggested that immune cells patrolled the body to identify and eliminate potentially cancerous cells by recognizing abnormal proteins or targets on the cells’ surfaces. These researchers explored ways to enhance this immune response in the clinic, at first by administering signaling molecules called cytokines to stimulate the proliferation of immune cells called T cells, and later by trying to genetically modify T cells to attack cancers.

A dramatic discovery by Stanford’s Levy in 1976 hinted at the possible payoff of harnessing the immune system in this way. Levy was studying a type of blood cell cancer called B cell lymphoma. B cells are white blood cells — cells of the immune system — that make antibodies to bind to invaders like bacteria or other pathogens. A protein complex called the B cell receptor is randomly generated from short protein segments every time a new B cell is born. That makes the B cell receptor on the cancerous cells a potent, cancer-specific target for the immune system. On Thanksgiving Day, 1976, Levy showed that it’s possible to create large quantities of antibodies to recognize and tag cancerous B cells for destruction.

The method worked, and some patients treated with the antibodies were cured. However, generating a unique batch of antibodies for each lymphoma patient proved too cumbersome. The scientists discovered that a less-specific target found only on B cells also worked well without requiring analysis of each patient's tumor. In 1997, the resulting drug, Rituxan, became the first FDA-approved monoclonal antibody for cancer treatment. Currently, several hundred thousand people each year receive the drug.

Antibodies alone have drawbacks, however. Although they float freely through the body, they serve primarily as red flags to trigger other cells of the immune system to kill their target. In contrast, T cells are efficient killing machines. But T cells are finicky. They only recognize proteins that are displayed in a particular way on a cell's surface. This safeguard keeps them from killing indiscriminately.

In 1989, Israeli scientist Zelig Eshhar, PhD, hit upon the idea of engineering a T cell with an antibody on its surface — a kind of a T cell-B cell hybrid that would combine the precision targeting of an antibody with the raw killing power of an activated T cell. Researchers at the University of Pennsylvania, Memorial Sloan Kettering Cancer Center, St. Jude Children's Research Hospital and the National Cancer Institute spent the next two decades optimizing the approach, which they termed chimeric antigen receptor T cells, or CAR-T, for use in humans. By 2010, the first case reports were trickling out: A lymphoma patient saw improvement; two of three people with leukemia went into remission.

"This is entirely unique," says Mackall. "It's something we cooked up in the lab. We've taken a powerful cell, and tricked it to go after a tumor by recognizing something it would normally ignore. And it turns out it works very well."

**I**N SOME WAYS, SAL WAS EXTREMELY LUCKY. STANFORD'S EARLY PARTICIPATION in the CAR-T trial was not a given. Shortly before his diagnosis in 2014, Davis, who was working primarily in the lab at that time, had a casual conversation with a Novartis liaison about the possibility of obtaining an experimental drug for her research into the biological causes of leukemias like ALL. She was hoping to identify markers on the surface of the cells that could be used to track the disease's origin and progression — perhaps helping to identify those patients most likely to relapse.

"She said 'Hey, you might be interested in this clinical trial we're running,'" says Davis. It was the CAR-T trial targeting a protein on the surface of B cells called CD19, and Stanford

became one of only five participating sites in the country.

As the administrators and physicians plowed through the months of paperwork necessary to enroll patients in the trial, however, Sal became very ill. In addition to the effects of the chemotherapy, he battled multiple infections that kept him in the ICU for over a month in November and December of 2014.

"We didn't know if he would make it through that period," says Aftandilian.

Sal was eventually discharged and seemed to be doing better. But the leukemia wasn't totally eradicated. Lumbar punctures revealed the presence of a few rogue leukemia



Immunotherapy experts Kara Davis (left) and Crystal Mackall

cells in his spinal fluid, and by April 2016 he had officially relapsed. A stem cell transplant was his next best option. Patients undergoing transplants receive high doses of chemotherapy to obliterate their cancer cells, but in doing so their own immune system is also destroyed. It's then replaced with the blood- and immune-forming stem cells from a healthy donor.

Sal had his transplant in June of 2016. But even that was unsuccessful.

"I remember so clearly getting the phone call about six months later telling me that Sal had relapsed," says Af-

tandilian. “I was with another patient at the time, but I hurried downstairs as quickly as I could. His family was devastated, as were we.”

**C**AR-T CELL THERAPY IS TIME-CONSUMING AND EXPENSIVE — the price tag of hundreds of thousands of dollars per patient limits access. Because Sal was participating in a clinical trial, there was no charge to his family. But researchers increasingly worry about how institutions, insurance companies and families will bear the cost of removing, genetically engineering and growing each patient’s T cells in the laboratory — particularly now that the FDA has approved the CD19-targeted CAR-T cells for clinical use.

Recently some companies suggested a middle ground: Families would be charged for the treatment only if it works. And, they point out, if successful, each patient may need only one treatment of the modified cells, with minimal additional medications to support the immune system.

“I think we’ll see a rapid evolution in the cost of the technology,” says Mackall. “Did we ever imagine that we would one day have cellphones that can do what they do for the amount we pay now? This is a new field, and it’s only going to get more affordable.”

Time and access are other sticking points. As demand for the treatment increases, it is becoming more difficult for existing, approved cell-manufacturing facilities to keep up. Currently it takes about two to four weeks from the time a patient’s cells arrive at the facility until the genetically engineered T cells are ready for infusion back into the patient — time in which physicians must battle to keep their acutely ill patients alive. In Sal’s case, this turnaround time, coupled with a technical glitch, nearly killed him.

“We collected his cells at the end of January,” says Davis, “and we kept him on a low dose of chemotherapy to keep his cancer at bay. But when his cells arrived at the manufacturing facility in New Jersey, they had been thawed. The container had somehow been damaged during shipping.”

“I was furious,” says Aftandilian.

‘I kept waiting every day for him to get a fever and he just didn’t.’ After a month, Sal had another check of his bone marrow to search for the presence of any leukemia cells.

“I wanted to go out onto the tarmac and yell at the baggage handlers responsible for transporting the cells. They could have easily cost Sal his life.”

At the end of February, the team tried again; in early April the modified cells were infused and Sal’s physicians were nervously watching him for any signs of ... well, anything.

“We were all so worried,” says Aftandilian. “I kept waiting every day for him to get a fever and he just didn’t.” After a month, Sal had another check of his bone marrow to search for the presence of any leukemia cells, and his care team finally let out their collective breath.

The cancer cells were gone.

“It was truly amazing,” says Davis. “Maria had tears in her eyes when we told her.” It’s been seven months, and Sal is back at school. “Right now he is cancer-free,” says De La Cruz. “I look at him and he seems just fine.”

**I**T’S TOO SOON TO TELL FOR SURE WHETHER SAL HAS BEEN CURED of his cancer. But other children have remained in remission for years. And researchers are working to improve cancer immunotherapy options for children and adults with all types of cancer. For example, Mackall is supervising a clinical trial in which the CD19-targeted CAR-T cells are combined with another type of CAR-T cell trained to seek out and attack another B cell marker called CD22. And Levy is investigating ways to combine the CAR-T cells with other immunotherapy approaches that block naturally occurring immune system checkpoints that prevent the immune system from tackling the cancer.

“The future is going to be in combinations of therapies that work together,” says Levy. “Right now, CAR-T therapy is a salvage therapy. It’s just a slice of the cancer immunotherapy pie, but it’s a big pie.” Levy envisions the possibility of genetically engineering the T cells within a patient’s body, eliminating the need to manipulate them in the laboratory and making the treatment faster, safer and cheaper because it would no longer have to be customized for each patient.

Meanwhile Davis and immunology graduate student Zinaida Good are looking for markers of B cell leukemia cells that correlate with the likelihood of a patient’s relapse after initially successful treatment. Recognizing patients likely to relapse could allow them to skip the grueling treatments and try immunotherapy sooner. “When I tell people that I treat kids with cancer, they often say, ‘How can you do that, it must be the saddest job in the world,’” says Davis. “But it’s not that to me at all. It’s a very hopeful job, particularly now.” **SM**

— Contact Krista Conger at [kristac@stanford.edu](mailto:kristac@stanford.edu)

Every Tuesday and Thursday after school, for about a month, Zack Dwyer, then 17, would settle into a reclining chair in the family room of his San Mateo, California, house and strap on a pair of goggles.

Attached to the eyewear was a smartphone containing an app that ran a virtual reality experience. It was designed by clinicians at Lucile Packard Children's Hospital Stanford to calm nervous teens like Dwyer, who was facing surgery to correct supraventricular tachycardia — rapid heartbeat caused by abnormal electrical impulses.

The virtual trip took him through the steps of the procedure, starting at the entrance to Packard and ending in the recovery room. He saw it all as if he was at the hospital — checking in at a desk, lying in a bed in the operating room, talking to a surgeon.

When the day of his surgery arrived, Dwyer took it all in stride, even when he was in the procedure room surrounded by a cadre of scrubs-clad physicians and nurses and a bunch of scary-looking machines. “It definitely would have been super overwhelming if I didn't know that was coming,” he says.

Adults usually know what to expect from a visit to the hospital. If they haven't undergone a medical procedure themselves, they've accompanied family members or heard about them from friends. To children and young adults, however, being in the hospital can be terrifying.

“Procedures and the hospital can be stressful for everyone,” says Lauren Schneider, PsyD, a pediatric psychologist at Packard Children's. “But for children, it's unfamiliar, a new life experience.”

The app Dwyer used is designed for teenagers, who make up the majority of pediatric patients undergoing the cardiac catheterization he had. Younger children present other challenges. They squirm when an intravenous line has to be inserted, scream during vaccinations and pull off anesthesia masks.

# virtual

## C A L M I N G

EASING ANXIETY IN YOUNG HOSPITAL  
PATIENTS USING IMMERSIVE  
TECHNOLOGY

BY MANDY ERICKSON

ILLUSTRATION BY GREG CLARKE



For these children, Packard doctors, nurses and child life specialists are employing technologically enhanced distraction techniques: virtual reality goggles that hide equipment and engage kids in games, and video screens that feature characters who trick youngsters into breathing anesthesia gas.

Packard physicians are also tapping the three-dimensional aspect of virtual technology to educate patients and their parents by showing them 360-degree images of organs. The systems illustrate medical problems in a way that drawings or verbal explanations never can and help young patients and their parents become more invested in their care.

### **MORE EFFECTIVE CALMING TECHNIQUES**

**F**OR YEARS, PSYCHOLOGISTS HAVE TALKED FEARFUL CHILDREN AND TEENS THROUGH FRIGHTENING PROCEDURES, nurses have offered stickers to appease preschoolers receiving shots and cardiologists have opened plastic heart models to show parents a congenital defect. But they are finding that new technologies including virtual reality and portable video systems are far more effective in calming, distracting and educating patients — easing the jobs of care teams while also reducing trauma for kids.

Schneider works with the pediatric cardiology division to treat children who are suffering from the emotional side effects of heart disease, such as fear of dying during a procedure or anxiety about palpitations. She provides in-person tours of the hospital and uses exposure therapy to help relieve their anxiety. She also teaches them relaxation techniques such as guided imagery, in which patients close their eyes and imagine waves crashing on a beach, for example. But she's not able to work with every patient, whether because they don't have time or because they live far from the hospital.

So she joined pediatric electrophysiologist Anne Dubin, MD, professor of pediatrics at the Stanford School of Medicine, in designing a simulation experience in which two teen actors, playing former surgery patients, walk young patients through the process (Emily addresses girls; Akilee, the boys).

Once they don the virtual reality goggles and start the program, patients see the entrance to Packard; if they turn their heads, they can see what's behind them. They move through the pre- and post-operative stages, viewing each room, complete with equipment and the care team. They also see the actors and physicians, standing off to the side, who explain what will happen at each stage. At two points in the experience, the real-life video of the hospital switches to a tranquil, animated scene.

## 'WE CAN PROVIDE

In one, the imagery becomes a nighttime valley, surrounded by mountains, under a sky filled with stars. With subtle shifts of their heads, patients can move dots of light around the scene; if they place the dot on the ground, it grows into a new tree. They can spend as much time as they'd like in the scene, building a forest, changing the color of the sky and meditating on the serene landscape.

"At key moments, when they're waiting, for example, and may start to feel nervous, they can bring up the memory of the forest-building," says Schneider, a clinical assistant professor of psychiatry and behavioral sciences. They can also practice breathing exercises, which are described at another point in the virtual program. Simply familiarizing themselves with the physical hospital reduces some patients' anxiety, she adds.

"Medical procedures can traumatize kids," Dubin notes. "Later in life, they may not be willing to undergo procedures they need. It colors their entire medical involvement and interactions."

### **A VIRTUAL OUNCE OF PREVENTION**

**W**HILE PACKARD'S SIMULATION APPS ARE HELPING TEENAGERS LIKE Dwyer relax before a scheduled surgery, younger patients benefit from the distraction provided by virtual reality goggles. Stephanie Chao, MD, turned to the technology when she needed to remove fluid from a cyst on the neck of her 9-year-old patient without any pain medication. She numbed his neck with ice, then had him put on the goggles before she produced the needle. "Most kids, just seeing the needle, would start crying," says Chao, an assistant professor of surgery. But her patient, engrossed in a 3-D animated underwater world of dolphins, shipwrecks and schools of fish, didn't even flinch when she poked him — twice: "He was so immersed in the virtual reality, he had absolutely no anxiety."

That immersive quality of the virtual experiences is what makes it so successful as a distraction tool: When they're looking into the goggles, patients can't see the equipment, blood or other frightening aspects of an exam room. They're also so taken by the novelty of it, they barely notice the needle pokes.

# A cool experience IN A SETTING THAT IS NOT COOL AT ALL.'

A team at Packard, working with game developers and using funding from the Lucile Packard Foundation for Children's Health and private donors, also created virtual games for precisely the kinds of situations Chao faced. Besides creating scenes like the one Chao used with her patient, the team created games that allow kids to play by moving only their heads. The games aren't likely to cause nausea, they aren't violent and they're continuous play, so they won't end just when a needle is about to enter a vein. In one of the games, patients zap burgers flying in space; in another, they steer penguins down a snowy hill.

"We can provide a cool experience in a setting that is not cool at all," says Veronica Tuss, who, as a child life specialist helps children cope with treatments in the hospital. "It really helps us get the child through the procedure."

Using adapted goggles that are readily sanitized, Tuss and the other child life specialists can choose games based on the patient's request: Some want to hear the game, some don't. Some are fine with a relaxing scene, while others require a high-activity distraction. The game developers are building a library of experiences — they have about 10 now — so Packard clinicians can choose the best one for each patient, based on age, personality and the procedure he or she is facing.

## MAKING SENSE OF CARE

**S**AM RODRIGUEZ, MD, A PEDIATRIC ANESTHESIOLOGIST WHO is part of a team developing these games, stresses that someone doesn't simply hand the kids a pair of goggles, then proceed with treatment. "We're still interacting with the patient," says the clinical assistant professor. "We ask them what they're seeing so we can gauge how they're doing. The interpersonal skills of the child life specialist, or the physician or the nurse are still very important."

For 3- to 4-year-olds who need to undergo general anesthesia, the Packard team has created a game, *Sevo the Dragon*, to convince them to breathe in the gas through their anesthesia masks. With a video screen showing the Barney-like dragon attached to their beds, the tots learn that *Sevo*

needs to cook pizza using fiery dragon breath, and they need to help! They blow into their masks, the child life specialists or the anesthesiologists surreptitiously tap a button, and *Sevo* blows fire onto the pizza slice.

"As soon as they blow out, they have to take a huge breath in," causing them to inhale the anesthesia, Tuss says. Soon they're asleep. Without a distraction like *Sevo*, younger children often pull the masks off their faces, forcing anesthesiologists to hold them down, "which can be a traumatizing experience for them."

"Having a terrifying clinical experience can change behavior for weeks," says Tom Caruso, MD, clinical assistant professor of anesthesiology, perioperative and pain medicine, also part of the Packard team developing the games. "We see sleep disturbances and regression in children's behavior."

The team is studying the effectiveness of *Sevo* and other games. From what they've seen so far, Rodriguez says, the games appear to make a "profound difference" among the most anxious children. "For some of these patients who've had a horrific experience in the past, it takes the fear from a 10 out of 10 to a 2 out of 10." No patients have yet shown any negative side effects from the goggles or the games, he says: "The worst case is the kid doesn't like it and takes it off."

Skyler Rodriguez, who is not related to Sam Rodriguez, liked her experience. Earlier this year, she had an osteoblastoma tumor on her spine that required surgery. Using virtual technology, her physician, Gerald Grant, MD, was able to show her and her parents a 3-D image of the tumor.

"He literally gave us a tour of my spine," the Hollister, California, 17-year-old says. "He showed me every possible angle, and what he would do during the surgery. It helped me understand what was going on, and what they would do. It made it less scary."

The system combines imagery from patients' CT, MRI and PET scans to create 3-D renderings through which patients can "travel," starting outside their skulls then proceeding all over their brains and into their spinal cords. Patients as young as 4 can see their tumors or a set of tangled arteries, or skull deformations. The brains and spinal cords appear in animated form, like three-dimensional textbook illustrations they can step into. They can also visually follow the steps

C O N T I N U E S O N P A G E 4 8

# GOING

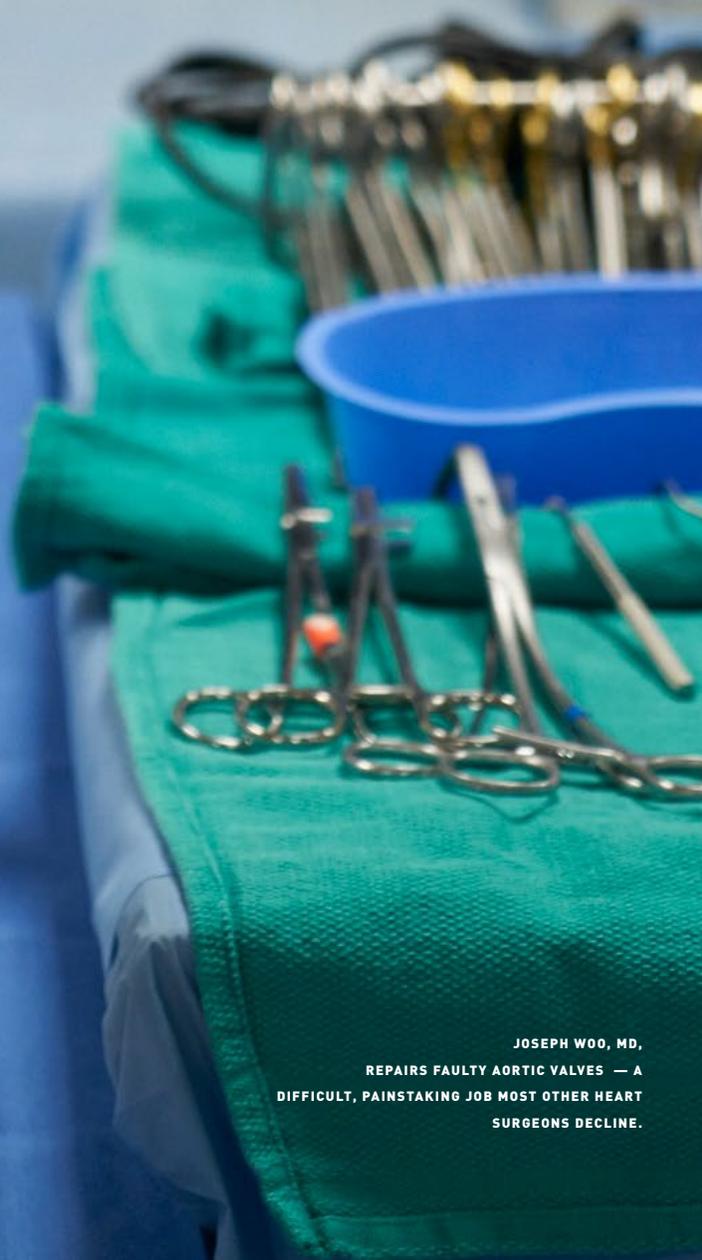
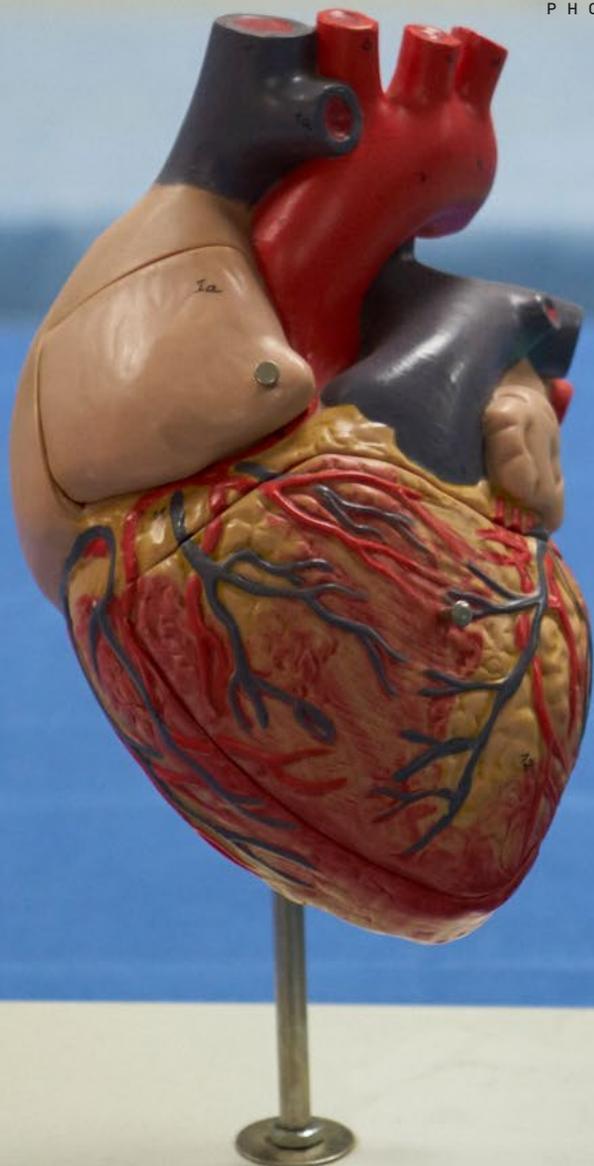
# NATURAL

USING HEART PATIENTS' OWN TISSUE TO  
REPAIR DAMAGED VALVES

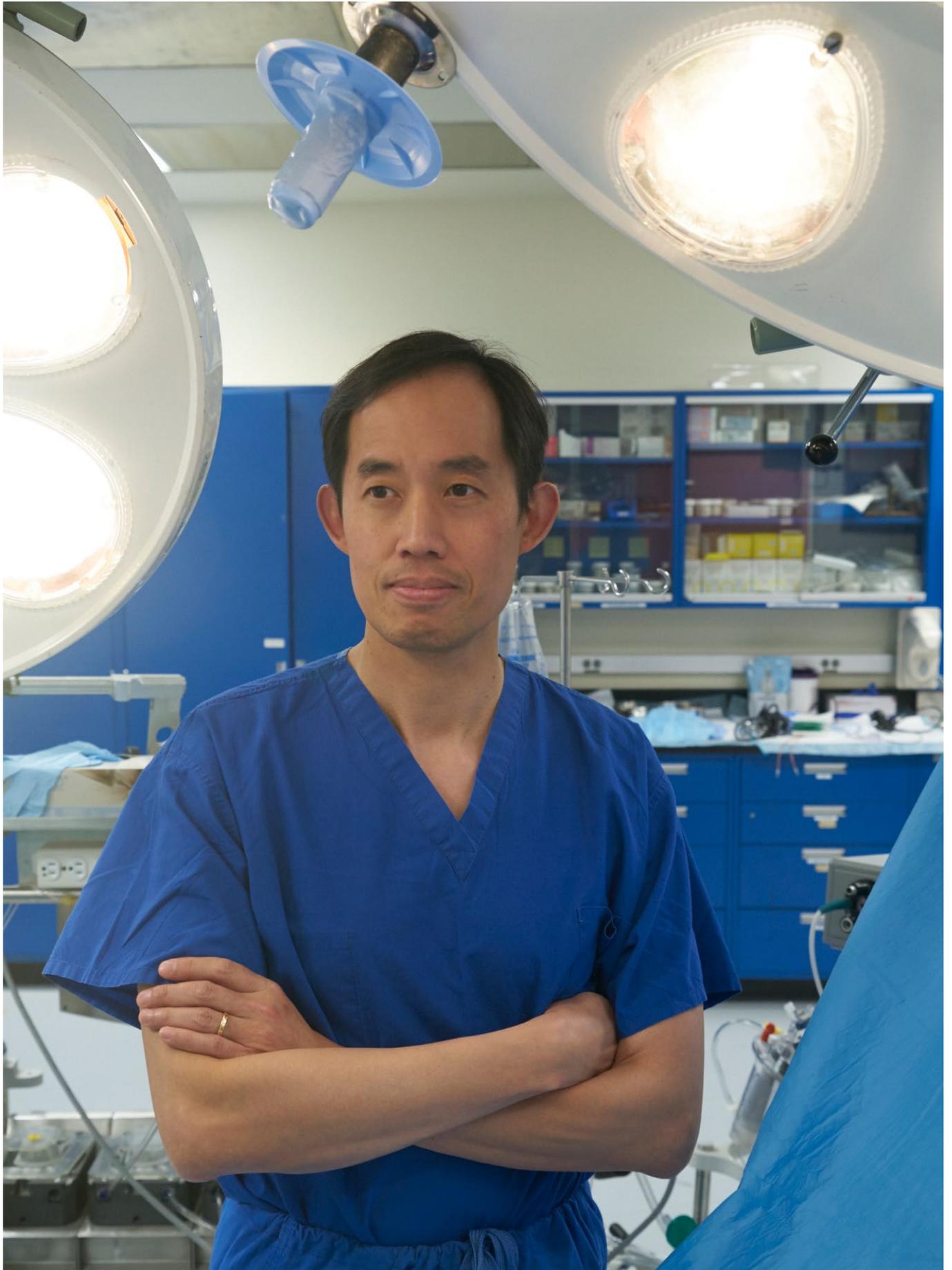
NATHAN HEALEY WAS IN THE PRIME OF HIS LIFE, a successful tennis pro who had been a contender at the Australian Open, when his heart erupted. A seemingly healthy 32-year-old, he was puttering around his house in Reading, Pennsylvania, keeping an eye on his newborn baby, when he felt a tightness in his chest. "All of a sudden, I felt dizzy and my heart rate was rising. I guess that is when something blew inside," Healey, now 37, recalled recently from his home near Sydney, Australia. "I sat down, calmed myself and called my wife. I said, 'I think I had a heart attack.'"

BY RUTHANN RICHTER

PHOTOGRAPHY BY LESLIE WILLIAMSON



JOSEPH WOO, MD,  
REPAIRS FAULTY AORTIC VALVES — A  
DIFFICULT, PAINSTAKING JOB MOST OTHER HEART  
SURGEONS DECLINE.



An ambulance ferried him to the local emergency room, where doctors found that a hole had ruptured in the center of his heart, releasing a stream of blood into his system. Healey was transferred to the University of Pennsylvania medical center, where the cardiac surgeon on call, Joseph Woo, MD, greeted him before midnight with some grim news.

“I remember hearing Dr. Woo say, ‘Chances aren’t good, but I will see what I can do,’” Healey recalls.

As Woo had learned, Healey was born with some previously undetected heart defects, including a weak spot that had progressively enlarged and finally burst open. He had other abnormalities in his aorta, including an aortic valve with three flaps of markedly different sizes, making it hard for the valve to close properly.

In the operating room, Woo faced an urgent decision: Should he try to repair the very malformed and defective valve using Healey’s own tissue, or should he replace it with a mechanical or animal valve, as was the standard procedure?

Woo knew that Healey’s athletic career would be over if he replaced the faulty valve, as the replacement options would not be durable enough or would require him to take lifelong medications that would limit his physical activities.

He decided to take the extraordinary step of repairing the valve, doing some creative sculpting. He remodeled the three oddly shaped flaps and used that tissue to fashion two flaps of equal size. He also rebuilt some of the surrounding tissues in a seven-hour procedure that saved Healey’s life and livelihood.

“It was an epiphany,” Woo, who in 2014 became the chair of cardiothoracic surgery at Stanford, says of the experience with Healey, which he later described in a 2013 case report in the *Annals of Thoracic Surgery*. “We’re always thinking, ‘How do you use what’s there and take advantage of it? That’s the fundamental concept to natural valve repair — to use what’s there in whatever creative manner you can to design something that works.’”

As with other surgical specialties, Woo says the growing trend among heart surgeons is to try to recycle, reuse, rebuild and preserve as much of a patient’s own tissues as possible, as patients generally do better when they don’t have to rely on synthetic or animal parts.

“For each of the heart’s components, we and others are developing ways to preserve the tissues and rebuild and resculpt them to take them from a diseased state and return them to a healthy state without removing or discarding things and needing to use artificial or animal substitutes. Your own tissues are alive and can heal and grow,” he says. “That is where we are headed.

“Mr. Healey’s situation is an extreme example where we really pushed this idea to the absolute limits and it was successful.”

That philosophy has put Woo in the forefront of the movement toward natural valve repair, which continues to evolve as surgeons devise new techniques and gain experience. Some in the cardiac community have been slow to embrace the idea, particularly when it comes to the aortic valve, which presents some challenges.

“Aortic valve repair is more complex than replacing a valve. It takes a longer time. It takes more skill,” says Arnar Geirsson, MD, associate professor and chief of cardiac surgery at Yale University. “I think in general cardiac surgeons probably do not repair enough of the valves that could be repaired. But I think eventually there will be more and more centers that specialize in these techniques, and eventually they will become more common.”

While aortic repairs are now being done only in a small number of medical centers with expertise and experience, some see them as the future of cardiac care.

“Aortic repairs are not as standardized and not as frequently performed, and they’re not as successful as mitral valve repairs, but there is progress being made now,” says Bruce Reitz, MD, professor emeritus and former chair of cardiothoracic surgery at Stanford. “I think that’s definitely the way the field is going.”

#### VALVE BASICS

**T**HE HEART PUMPS BLOOD in only one direction, with the heart valves helping to maintain the flow as part of a well-coordinated choreography. With each heartbeat, the valves open and close their flaps, known as cusps or leaflets, first releasing the blood and then closing their doors to prevent it from flowing backward.

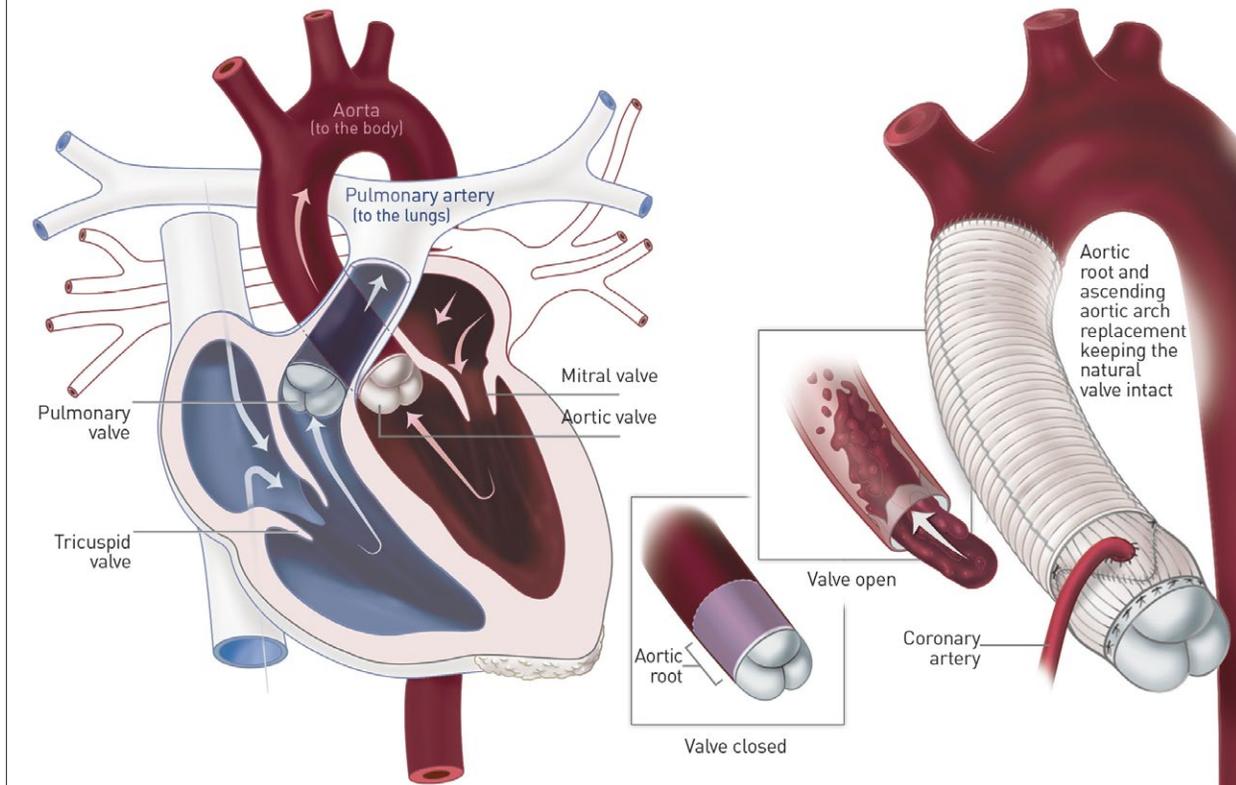
The process is regulated by the four heart valves — the aortic, mitral, tricuspid and pulmonary — which open and close as many as 100 times a minute. While all the valves can become diseased, the mitral and aortic valves are most prone to problems, as they control blood flow on the left side of the heart, which carries the heaviest load.

The mitral valve helps move blood from the heart’s upper to lower left chamber and over time can become damaged because of intrinsic genetic abnormalities or through wear and tear. The leaflets may turn floppy and lose their ability to close properly, a condition known as mitral valve prolapse. When a prolapsed valve allows blood to flow backward, surgical intervention may be needed. The valve also can be damaged by a buildup of calcium or plaque, which narrows the space and restricts blood flow, putting excessive demands on the heart.

The aortic valve is the final gateway for blood as it leaves

## ONE WAY TO FIX A HEART

In an aortic root and ascending aortic arch replacement, surgeons replace the damaged section of the aorta with a Dacron tube and sew the aortic valve into the tube's end. The valve's three leaflets open and close with each heartbeat to allow the flow of blood out of the heart.



the heart and enters the bloodstream. It is also prone to prolapse and leakage as well as narrowing from calcium buildup, which can thicken and harden the tissue and limit blood flow. This latter condition, known as aortic stenosis, is most common in older adults.

Rheumatic heart disease used to be a common cause of valve problems, and, while still prevalent in developing countries, it has all but disappeared in the United States. Intravenous drug abuse, spurred by the opioid crisis, has become a more common source of valve infections and a growing problem in this country, says cardiac surgeon Duke Cameron, MD, at Massachusetts General Hospital in Boston. Finally, valve problems can result from structural birth defects — the source of Nathan Healey's crisis.

In the early days of valve treatment, clinicians tried to repair the damaged structure, but had little success, in part because of technological limitations, including the lack of imaging tools to gauge valve leakage, Cameron says. The

1960s then saw the introduction of mechanical valves that enabled doctors to cut out the diseased tissue and replace it with a substitute made of mechanical parts, similar to the valves found in car engines, Woo says. These early versions consisted of a grape-sized ball of plastic inside a metal cage that opened and closed to allow the blood to flow through. These prototypes were improved over time, with more sophisticated versions now made of biocompatible metals such as carbon or titanium.

Mechanical valves are effective and can last a lifetime, but they have a major drawback in that blood tends to stick to them and form clots. Patients with mechanical valves have to take blood-thinning medications, which require regular monitoring to avoid excessive bleeding and stroke.

In the 1970s, another alternative came to the fore: valves taken from pigs or cows. These can work well, but aren't as durable, particularly when used in younger patients who have greater heart demands. Animal valves can wear out in 10 to 15 years, so

patients have to undergo a second replacement and endure the risks of another surgery. Animal valves also carry a small risk of infection, which happens in about 1 percent of cases a year, Reitz says.

Because none of these replacement options is ideal, surgeons have turned to creatively restructuring damaged valves, using the patients' own tissue.

"The idea of valve repair has come back because we've lived with these artificial valves for several decades and are beginning to appreciate their limitations," Cameron says. "Most people don't want to return for more surgery, and they don't want to take blood thinners. The gauntlet's been thrown down to do a better job of repairing valves so patients can have a good quality of life and have fewer reoperations."

In 1983, noted French surgeon Alain Carpentier, MD, PhD, published a landmark paper in the *Journal of Thoracic and Cardiovascular Surgery* in which he described his repair technique, known as the French correction, for mitral valves. He advocated cutting away portions of the diseased structure; shortening the cordlike tendons that help support it and connect it to the left ventricle; then stitching a metal and fabric ring around the base to give it stability.

His work was followed by other developments in the field, including the use of Gore-Tex to create new cords to suspend the valve and to rebuild some of the supporting structure. These innovations led to a surge in the popularity of mitral repair. A 2009 study of some 58,000 patients found the number of repairs done between 2000 and 2008 rose from 51 percent to 69 percent. At the same time, use of mechanical valves fell from 68 percent to 37 percent, according to the report, published by the Society of Thoracic Surgeons.

Multiple studies have shown that patients who undergo mitral valve repair do better overall: They are more likely to survive, spend less time in the hospital and suffer fewer complications, such as infection and stroke, compared with those with substitute valves, whether animal or mechanical.

"With the mitral valve, the data is quite clear. If you can repair, it's better. You have better survival," says Geirsson at Yale. "I think once the techniques are improved, that is what is going to happen with the aortic valve."

The guidelines of the American College of Cardiology and the American Heart Association recommend repair for certain mitral valve problems, such as a prolapsed valve, but for other conditions it leaves the decision largely to the surgeon's discretion, says T. Sloane Guy, MD, associate professor of cardiothoracic surgery at Weill Cornell Medicine. For aortic valve repair, the guidelines are more vague, indicating repair can be considered in "appropriate patients, where good results are expected," Guy says.

#### FIXING THE AORTIC VALVE

**T**HAT'S BECAUSE THE aortic valve is a totally different animal, both in form and function. For instance, while the mitral valve has two leaflets, the aortic valve has three, so a surgeon has to effectively line up three sides for the valve to work well, Woo says. There is also less tissue to work with in an aortic valve repair, and different techniques and finer sutures are needed, he says.

With these challenges and a steep learning curve, aortic valve repair has been slower to catch on.

"It's not been nearly as successful or widely adopted because it's really a fundamentally different kind of valve, and the results haven't been as good as mitral valve repair. It really depends on the nature of the particular valve and the particular patient," says Guy, who encourages patients to go to a center that focuses on repair and has a high volume of cases.

In 2016, Cameron penned a commentary in the *European Journal of Cardio-Thoracic Surgery* in which he lamented the elusive nature of aortic valve repair, calling it a "difficult nut to crack."

"But there is renewed interest and considerable progress on this front," he notes, spurred in part by the pioneering work of two surgeons, Tirone David, MD, and Sir Magdi Yacoub, MD. In the 1990s, they developed procedures to

## 'THE GAUNTLET'S

## BEEN THROWN DOWN

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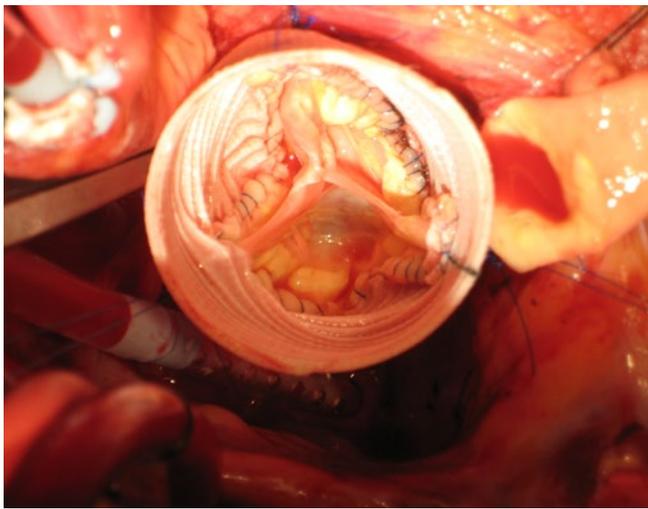
preserve the valve in patients with aortic aneurysms, or a bulge in the aorta that can cause it to rupture. The procedure, known as valve-sparing root replacement, is most commonly done in patients with Marfan's syndrome, a connective tissue disease that can impact the heart, as well as patients with high blood pressure that has led to enlargement of the base of the aorta, known as the root.

In the procedure, surgeons cut out the diseased part of the aorta and replace it with a tube of Dacron polyester, known as a graft, which is stitched to the heart. Instead of cutting out the aortic valve, as was done in the past, surgeons preserve the patients' tissue and reimplant it inside the new tube, sometimes refashioning the valve to fit the space. The procedure is made more complicated by the fact that the surgeons have to detach the coronary arteries, which flow from the aorta, and then reattach them once the new graft is in place.

#### IN THE OPERATING ROOM

**O**N A RECENT SEPTEMBER MORNING, Woo is called in to perform a variation on this procedure at Stanford Hospital in a man in his 50s who has endocarditis, a heart infection, which has damaged his aortic valve and aorta. The patient is put on a heart-lung bypass machine, which temporarily stops his heart and takes over the function of his heart and lungs while the surgical team does its work. Before Woo begins, he views the heart on an echocardiogram, displayed on a nearby screen. It shows the valve leaflets flopping back and forth. "Wow, there's significant leaflet destruction there," he says.

He and his team, including David Scoville, MD, chief resident in cardiothoracic surgery, begin by cutting out the defective aortic root, then meticulously excising 20 small fragments of diseased tissue from within and around the faulty valve. They replace the aortic root with an inch-wide Dacron tube, which they anchor in place with multiple blue nylon sutures. Then comes the most challenging part — sewing what



**AN AORTIC VALVE** as seen during a surgery to repair the valve and replace a diseased section of the aorta. The valve, with its three leaflets pulled together, sits at the base of the ribbed Dacron tube replacing the diseased aortic tissue. Dark sutures stitch the valve's edges to the inside of the tube.

remains of the patient's valve back inside the tube.

"Imagine tailoring a suit but from inside the suit," says Woo, as he does some customized tailoring inside the narrow tube, stitching the valve in place and shaping it with fine Gore-Tex sutures so the cut leaflets are reassembled and then evenly aligned. The process is painstaking: He carefully loops in the thin threads, using fine tools. It's a procedure many surgeons won't attempt, as there is very little valve tissue left to work with. But for the patient's sake, Woo is determined to make it happen.

He and his colleagues then create two small holes in the graft to reattach the coronary arteries. They begin with the left main coronary artery, which Woo lightly calls "the seat of the soul," as it carries blood to nourish the muscles of a vital heart chamber which pumps blood to the entire body. They then reconnect the right coronary artery and pressurize the repaired aortic valve while surveying the results on the imaging screen, which shows a normal valve opening and closing with leaflets neatly lined up.

"It's opening up nicely and closing beautifully," Woo says after a process that takes more than four hours. "This patient will keep his own valve over time."

A few weeks earlier, Woo tackles a different type of repair, fixing a mitral valve in a patient in his 60s who has had a prolapsed mitral valve for decades. Recently, the man began to have problems, including shortness of breath and palpitations, with tests showing the valve is leaking blood. In the operating room, the patient is put on a heart-lung bypass machine, but instead of opening up the chest, Woo is able to use a minimally invasive approach, accessing it from the side through a 2-inch incision between the ribs. This approach is as effective as operating through a major incision in the chest and reduces complications, pain, blood loss, infection and scarring, as well as time spent in the hospital, he and Andrew Goldstone, MD, a cardiac resident, reported in a 2016 review paper published in *Annals of Cardiothoracic Surgery*.

C O N T I N U E S O N P A G E 4 9

# CURING OUR

# CLIMATE

WHY WE SHOULD SHOUT ABOUT ENVIRONMENTAL  
CHANGES THAT ARE MAKING US SICK

In musing about the impact of global environmental change on the human race, Paul Auerbach, MD, and Jay Lemery, MD, mostly steer clear of politics. They admit they aren't climate experts. They are, however, experts in treating people who suffer sometimes devastating health outcomes that are caused or exacerbated by global changes in the environment.

Auerbach is a professor of emergency medicine at Stanford and a leading authority on wilderness medicine, and Lemery is an associate professor of emergency medicine and chief of wilderness and environmental medicine at the University of Colorado.

In a new book, *Enviromedics: The Impact of Climate Change on Human Health*, published by Rowman & Littlefield, they lay out “our inventory of adverse health impacts” of environmental change and call on physicians to undertake a Herculean effort to raise awareness of the problem to help preserve human health.

They evoke climate justice as a means to approach the issue, arguing that negative impacts of climate change on people undermine their rights, as laid out by the United Nations, to a standard of living that is adequate for their health and well-being.

“We should be planning for the future not only as if our lives depended upon it, but knowing full well that the lives of forthcoming generations depend upon it. Medical justice demands this approach,” they write.

The ramifications of environmental events are clear, Lemery and Auerbach say. Floods, for example, account for about half of weather-related disasters, affecting 2.3 billion people worldwide during the past 20 years, while droughts kill more people, accounting for 59.6 percent of deaths caused by extreme weather events.

The authors use fictional stories of composite patients — whose symptoms mirror real ones — to illustrate afflictions people suffer because of environmental factors.

One man spends two weeks at the beach in New Jersey that had been a childhood haven, but this time biting flies and mosquitoes are relentless. Three weeks later, he has a fever, headache and vomiting. After his symptoms worsen, a doctor skilled at detecting diseases formerly considered tropical diagnoses him with malaria.

I L L U S T R A T I O N B Y G R E G C L A R K E

A 93-year-old woman refuses to leave her apartment when temperatures soar above 90 degrees for 10 days. An electrical brownout knocks out her air-cooling system and she doesn't want to drink tepid water. So she stops taking her heart medication. Eventually, her heart and nervous system shut down and it is too late to save her.

The authors also point to natural disasters like this year's hurricanes Harvey, Irma and Maria. The onslaught of rain and wind kills or injures people. Power outages shut down hospitals. People must abandon their homes. Flood waters become a toxic stew of human and chemical waste. Stagnant water near populated areas spreads mosquito-borne diseases. Finally, emotional trauma manifests itself through stress, depression and anxiety for years to come.

In the following excerpt, Auerbach and Lemery advocate for physicians to be ambassadors in making everyone — individuals, lawmakers and industrial leaders — aware that stopping or reversing the negative effects of climate change on human health is an urgent matter.

A D O C T O R ' S A P P R O A C H

*We are doctors who care for our patients, and the planet that is their home. We wrote this book because we believe that humans are making changes to our environment that soon may become irreversible. We fully understand that the science of climate change is evolving as experts make more observations, perform more research, derive more data and do their best to make reasonable interpretations. The controversy is apparent, but the logic of preserving what we can and trying to avoid depletion of resources and immutable changes to our planet that will affect human health adversely are truths to us. We took a “doctor’s approach” because we believe we are facing a sick patient and we want emphatically to bring human health to the top of the discussion. We presume it is highly likely that humans are altering the environment in a way that causes global warming, widespread pollution, destruction of habitats and everything that comes with these. From that assumption come logical human health implications and you are entitled to know about them.*

*We care about you. If your chest was hurting, you couldn't*



breathe and your pulse was undetectable, we wouldn't sit still and ponder the situation. We'd do everything possible to make an accurate diagnosis and try to save your life. We'd act fast, because we know that moments count. Should we be any less concerned about our planet? The current situation in Glacier National Park is instructive. In our children's lifetime, it may need to be renamed Glacier-less National Park. Does that matter? We believe it does.

We rely upon the science of others to understand predictions of global climate change, but we do not need others to explain the health effects that logically would be related because these are conditions we know. We treat them. The composite patients suffering from post-flood diarrhea, wildfire-induced shortness of breath and heatstroke-induced organ failure are the same cases seen every day in emergency departments and medical wards around the globe. Climate change will add to the burden of disease, and sooner or later it will affect people you know, and hundreds of millions you never have met.

Part of the problem to date with science communications on climate change has been failure to identify an immediate health threat. Without that stimulus, the imperative to change the way we live and consume our resources is not sufficient. Lacking a perfectly accurate crystal ball is an impediment for some to become engaged in this issue. We want everyone to form an opinion, and to act on their knowledge and conscience.

If you disagree with our premise, then learn and respond. Throwing up your hands in frustration over the futility of our future will not solve anything. Consider recent events. Fifty years ago, 42 percent of Americans smoked cigarettes. Although tobacco use was widely suspected to cause lung disease, the national per capita cigarette consumption had been on the rise since the 19th century. Medical scientists pointed out the hazards. However, the industry sponsored efforts to suppress the science about detrimental health effects. Such was the state of affairs that some physicians themselves became spokespersons about the benefits of cigarette smoking.

Today, only just over 17 percent of adults in the United States call themselves smokers. How did this change? For one thing, the financial cost of smoking became prohibitive

(economics). Tobacco smoking was banned from public places (regulation). A relentless public health media campaign (medical science) made it impossible to ignore the fact that smoking causes major health risks (public opinion). Although this may not be precisely how to affect changing attitudes and behaviors regarding climate change, it clarifies two things. When effects from a behavioral pattern can be determined and linked to a negative economic or health risk profile, public behavior can change. Furthermore, seemingly insurmountable situations that require support of the masses can be overcome.

**THROUGHOUT THE BOOK, LEMERY AND AUERBACH EXPLORE** health impacts of climate changes they say redefine "normal" with wet places becoming wetter and dry places becoming drier. In the western United States, that can mean longer wildfire seasons.

During peaks, smoke filled with gas and fine particles of building materials, vegetation and chemicals can travel thousands of miles, causing a host of maladies in its path that can linger for months. People in smoky areas commonly experience coughing, shortness of breath, sore throats, irritated eyes, runny noses and sinus pain. Symptoms can be especially severe for those with lung conditions, elderly people and children.

In the following excerpt, the authors tell a story that mirrors stories about recent Northern California fire victims. Tom and Sally live in a log cabin near Bend, Oregon. He had been a volunteer firefighter — they know how to prepare. When dry lightning sparks a blaze 5 miles away, they pack to leave. Evacuating friends stop to check on them on their own way out. "We'll be right behind you," Tom replies. That is the last time their friends see them.

#### **NOT A LESSER FIRE**

*The wall of fire came hard, fast, and unexpectedly from two directions. The inferno burned or melted everything in its path. By the time Tom realized that Sally was not responding to his shouts, she was face down in the backyard, crushed by a fallen tree limb. In less than five minutes, she was burned beyond recognition. In a desperate attempt to save himself, Tom quickly dug a shallow pit in the ground, knelt down and covered up with an old silver "space blanket." In a lesser fire, this might have saved his life, but this was no lesser fire. The scalding air and*

*flames made quick work of Tom, and destroyed his home and thousands of acres of surrounding forest. It was one of dozens of fires triggered by the same weather system, in a pattern that would be repeated more often as weather and fuel combined to create a perpetual fire hazard.*

The authors continue: *Extreme weather events are disruptive and almost always hazardous to human health.*

*From the perspective of those who need to decide whether to take actions that will diminish the likelihood of such events, it is mandatory to understand what they are, how many people they affect and what would be the benefit to humankind if we were able to cause them to be fewer, less intense and of shorter duration.*

*Knowing how to survive a wildfire or flood is not nearly as good as not having to endure them. SM*

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#### **FEATURE**

##### **A healing environment**

**CONTINUED FROM PAGE 14**

"Both sides of the equation were critical to creating a healing space."

Physicians, nurses and other health care team members evaluated where equipment would be placed and whether there was enough room to maneuver when treating children in their rooms, and weighed in on aesthetic details. When pediatric anesthesiologist Chandra Ramamoorthy, MD, saw that some rooms were painted periwinkle blue, she instantly knew they would need to be changed. In the blue rooms, it would be difficult to ascertain between the reflection of the wall color and cyanosis — a bluish discoloration in patients whose blood isn't getting enough oxygen.

"We had initial designs in place for the room mockups, and I don't think a single thing stayed the same," Sullivan says. "Every design choice for the new building was made with the intent to put autonomy and control into the hands of children and families, staff and providers, and frankly we wouldn't have thought about these details without engaging the staff and the families who will actually be using the space."

## STIMULATING THE MIND, RESTORING THE BODY

Finally, priority was placed on families being able to connect the worlds of learning and healing, mind and body, resulting in a space that includes abundant access to nature, art installations, play spaces and other interactive elements.

"You're always trying to engage your child in something when you're in the hospital. When my son had to fast before his surgeries, we would walk the halls to try to keep his mind off his hunger," Flynn says. "We'd stop at the art on the walls and play 'can you find' games. Bringing in art and other elements of interactive play like this to the new hospital was crucial."

Thematically, opportunities to learn about the local environment and nature themes are prominent across the campus. Paths of animal footprints native to California are implanted throughout the hospital's gardens for visitors to follow and learn about the state's diverse wildlife. The main elevator core on each level of the new facility is built to look like a tree growing through the center of the building, clad in reclaimed old growth redwood salvaged from the deconstructed Moffett Field hangar in Mountain View, California.

Aspects of California's ecosystems are also part of the foundation for the building's visual "way-finding" system, implemented to help direct people through the building. Stanford University ecologists and patients at the existing Packard Children's Hospital helped select two animal "ambassadors" native to each floor's eco-region. Sculptures of them are tucked into stone niches along the main entrance and are repeated near the elevators and in colorful signs on each floor, helping families find their way around. Patients — and their siblings — also helped the design committee select interactive play structures for the hospital's gardens and large animal structures that serve as directional landmarks on each floor. Artist Sherri Warner Hunter conducted workshops during which patients created crayon and oil pastel drawings of rocky shore creatures, and the drawings have been turned into mosaics that are inset on the underside of several of the play structures and furniture in the garden.

"This is a Northern California hospital in a place where people value preservation of species and nature. It was important to create a building that exhibited stewardship of

those values," Guenther says.

But an element of whimsy fit for children remains. At first, the inclusion on the third floor of a life-size sculpture of a pair of hadrosaurs — the only known dinosaurs to live in Northern California — worried parents on the design committee. "We were concerned that a dinosaur would be scary to little kids," Flynn recalls. So at the suggestion of the design committee, the dinosaurs are wearing bunny slippers to make them look more friendly.

Indoor playrooms on each floor, designated by age group, provide spaces for pet therapy, arts and crafts, group games and other activities that involve the whole family.

"There is endless evidence that supports the medical need for healing elements in the hospital. But at the end of the day, what makes it work is that it feels very human. What we wanted was an expansion of Lucile Packard's original vision that would not lose the charm and the humanity of the original," Guenther says.

"As a parent who has had a sick child, any time you step foot into a hospital it brings back a rush of emotions. Some good, some challenging," Flynn reflects. "For me, despite the difficult memories, I always had this feeling that the hospital was a pleasant place to be and I tend to get filled with an overwhelming amount of gratitude for that. I keep envisioning my son in the new space at 2 and 3 years old. He would have absolutely loved the new garden, the sculptures, the opportunity for exploration."

Wayman echoes that: "Parents bring the lived experience with them. They've walked the walk with their children. While care teams' lived experience is providing care and they have an invaluable perspective on the safety and efficiency of the new design, families look at it with heart. And no one else can do that." **SM**

— Contact Kate DeTrempe at [KDeTrempe@stanfordchildrens.org](mailto:KDeTrempe@stanfordchildrens.org)

## FEATURE Ultrasound solution

**C O N T I N U E D F R O M P A G E 1 9**  
these diseases, existing therapies have drawbacks that the Stanford team thinks focused ultrasound may be able to circumvent. In sarcoma treatment, for instance, recent advances in radiation, chemotherapy and surgery haven't improved patient sur-

vival; the scientists hope folding focused ultrasound into the mix will yield better results for patients in the long run.

A major impediment to using focused ultrasound more widely is that, with the exception of the small number of FDA-approved applications, insurance doesn't routinely cover it. Fighting for insurance authorization, sometimes through several rounds of appeals, can be time-consuming. Although some children are now treated through clinical trials, finding patients who are good candidates for research and are willing to participate can be a slow process.

"It's also technically challenging," Ghanouni adds. The team giving the treatment needs to understand the complex physics of ultrasound — how to blast sound waves from several different points of origin so that they converge, in phase, on the problem tissue — as well as how to correctly monitor the procedure with MRI, the medical details of each condition being treated and how to provide appropriate anesthesia for many types of patients. Bringing all these areas of knowledge together requires the expertise of a place like Stanford.

"It's not plug-and-play," Ghanouni says. "Frankly, focused ultrasound has needed some champions."

## CHALLENGE OF BRAIN TUMORS

The brain, however, is the most challenging frontier. The thick, uneven skull bone sends sound waves off target, so radiologists must have a detailed CT scan of the patient's skull to figure out how to compensate for deflections caused by its topography. An additional complication is that sound waves travel through bone 20 times less efficiently than through soft tissue, heating the bone as they traverse it. Before the therapy, patients must have their heads shaved to prevent trapping air bubbles near the bone that further exacerbate sound wave deflection; they must also wear a cap filled with chilled water during treatment to keep the skull evenly cooled.

These problems have been addressed in adults — who can receive focused ultrasound for such diagnoses as essential tremor and Parkinsonian tremor — and now researchers want to bring the potential benefits to children with neurological conditions. Ghanouni and Stanford neurosurgeon Gerald Grant, MD, are collaborating with others at Nicklaus Children's Hospital in Miami to conduct

a trial for children with tuberous sclerosis, an inherited disease that causes tumors in many organs. Some patients develop benign brain tumors called subependymal giant cell astrocytomas, or SEGAs.

"These tumors are in the water spaces, the ventricles, in the brain. They can grow and obstruct the brain's plumbing," says Grant, associate professor of neurosurgery at the School of Medicine and division chief of pediatric neurosurgery at Packard Children's. The tumors are operable, but treating them surgically requires cutting through healthy structures to reach them. Depending on the exact size and location of the SEGA, a child's memory tracts may be damaged, or the corpus callosum, which connects the two halves of the brain, may have to be severed. Recovery from surgery takes three to six weeks, and the surgery increases the patient's risk of seizures later on.

Against that background of risks for more accepted treatment methods, focused ultrasound is appealing. Because SEGAs are benign, controlling but not completely eradicating the tumor may be acceptable. In addition, SEGAs have well-defined edges on MRI scans and few blood vessels, characteristics that make them a good fit for treatment with focused ultrasound.

Cancerous brain tumors are more challenging targets. They tend to have long fingers that infiltrate healthy brain tissue and are fed by many blood vessels. These blood vessels create a hazard for focused ultrasound because accidentally severing one could create a deeply buried brain hemorrhage that would be hard to control.

But there may still be a role for focused ultrasound in brain cancer treatment; scientists at other institutions are experimenting with using it to temporarily open the blood-brain barrier to let chemotherapy drugs enter the brain. The Stanford team also has plans to conduct trials of this technique. Some teams have also packaged chemo drugs inside liposomes (bubbles of fat) that could be melted with focused ultrasound to release drugs where they're needed and minimize side effects elsewhere in the body. The technique is promising for tumors growing inside and outside the brain.

In the meantime, Grant and his collaborators will proceed cautiously in testing whether focused ultrasound can help kids with SEGAs. They'll look for patients who

would otherwise require invasive surgeries and whose imaging scans show tumors the technique could safely hit.

"We'll advocate for trying this because, in the right cases, where it is safe and could improve the child's quality of life, we wouldn't feel like we would have much to lose," Grant says.

#### A HAPPY KINDERGARTNER

Cadence's outcome is promising. Late last year, her desmoid grew again — it had been about 15 ml in volume after the first treatment, but expanded to 24 ml — so she returned to Stanford for a second focused ultrasound treatment in December. The entire trip took four days, and Cadence was making snow angels and sledding with family soon after.

Ghanouni plans to keep zapping the center of the lesion as needed to prevent it from interfering with Cadence's life. In addition to the teenagers treated before Cadence, Ghanouni has also treated 32 adults with desmoids and says other patients have begun to seek him out after reading about the Stanford team's early results in online support groups.

For the long term, Ghanouni hopes another scientist will develop a treatment that vanquishes desmoids for good. "There are some exciting drugs on the horizon with promising results for desmoids," he says. The longer he can help children like Cadence avoid amputations, radiation and chemotherapy, the more options they will have later, he adds. "Focused ultrasound doesn't burn any bridges for these kids."

Today, Cadence is a happy kindergartner who is excited by Ghanouni's "magic tools" but who otherwise doesn't mention her desmoid much. To her, it's just part of her arm.

"This summer, another girl at swim lessons asked, 'What's that on your arm?'" her mom recalls:

"It's my bump," Cadence told her.

"How did you get it?" the other child asked.

"I was born with it," Cadence said. Then, after a minute, she added, "I don't want to talk about it anymore." "OK," said the other girl.

Then they jumped into the water, two little girls at any swimming lesson anywhere. They floated. They kicked. They stretched their arms above their heads, dug into the water, and learned how to swim the backstroke. **SM**

— Contact Erin Digitale at [digitale@stanford.edu](mailto:digitale@stanford.edu)

## FEATURE

### Virtual calming

CONTINUED FROM PAGE 37

surgeons will take to remove tumors, correct deformations or place electrodes to treat epilepsy.

Before the virtual experience, says Grant, young patients are often disengaged and frightened. "It's hard to connect them with what's going on," he says. "They're scared of pain, they're scared of waking up during the surgery, they're scared of dying." But when they view the 3-D imagery, "You see the kid light up. They start asking questions. Especially the teenagers. It reduces the fear, the anxiety, the mystery."

While there is no data to show that educating young patients about their medical situation leads to improved results, "They feel more stable; their approach is more relaxed. It enhances their trust," says Grant, an associate professor of neurosurgery. Without the imagery, he adds, they can't fully understand the problem and how the surgeon will correct it.

Pediatric cardiologists are also using the technology to educate: David Axelrod, MD, is building a library of virtual imagery that illustrates congenital heart defects. Unlike the neurology cases, these defects tend to fall into categories, so he can pull up virtual experiences to explain a specific condition or defect and what the surgeons will do to fix it, all in 3-D.

"It's really important for families to know what's going on with their child's heart defect," says Axelrod, a clinical associate professor of pediatrics. "The 3-D images give them a much better understanding."

The program that calmed Zack Dwyer's nerves is being used in a pilot study that Schneider and Dubin are conducting to see if it reduces anxiety for 8- to 25-year-old patients who are undergoing cardiac catheterization surgery. If it does, Packard plans to produce virtual programs for young patients who require different cardiac treatments and, eventually, any stress-inducing procedure.

Dwyer, who first noticed his racing heart during basketball practice at San Mateo's Hillsdale High, was back on the court 10 days after his surgery, the rapid heartbeat just a memory. He says he would strongly recommend the app experience to other teens. Taking the virtual tour led by Akilee, "a kid my age," helped him a lot. "It's crazy to think you have to have heart surgery," he says. "But I had

something that made it seem like it was no big deal." **SM**

— Contact Mandy Erickson at [medmag@stanford.edu](mailto:medmag@stanford.edu)

## FEATURE Going natural

CONTINUED FROM PAGE 43  
Woo and his colleagues, including cardiac fellow John MacArthur, MD, operate through this small opening, reviewing their progress on the video screen. The mitral valve comes into view — the leaflets looking like puffs of pale, loose tissue. "A lot of surgeons will cut this out," Woo says. "We are going to resculpt these leaflets to make them as normal as possible."

Using a procedure he devised, Woo uses a single Gore-Tex suture to further anchor the valve in place and secure it to the wall of the ventricle. He folds in the excess tissue from the leaflet to prevent it from prolapsing again. He then takes a titanium ring covered in dark fabric and stitches it down around the base of the valve using spaghettilike sutures. The procedure tightens up the valve and eliminates the leakage.

Once done, Woo reviews his handiwork on the imaging screen, confirming that there is no backflow of blood — the valve is effectively repaired. He is intensely focused and works efficiently, so the whole process takes about an hour and a half, making a procedure that can take some surgeons as much as six hours look relatively easy. In a 2013 study in the *European Journal of Cardio-Thoracic Surgery*, he and MacArthur found that patients undergoing this version of mitral repair spent only 59 minutes on a heart-bypass machine, almost half the usual average, and did very well. This patient of Woo's recovers nicely and is able to leave the hospital four days later.

In general, surgeons tend to develop their own variations on these repair techniques, depending on the patient's anatomy and the availability of tissue for resculpting. Unlike other clinicians who are subject to rigid guidelines in prescribing drugs and other treatments, surgeons have a great deal of leeway in adapting their practices based on what they encounter in the operating room.

### ALL-REPAIR PHILOSOPHY

Woo says he likes to approach each patient as a candidate for repair, though he real-

izes it's not always possible. For instance, in patients with valve fibrosis, the leaflets may be so thickened and damaged by calcium deposits that they can't be manipulated and preserved. But he is nonetheless guided by an all-repair philosophy.

"We believe, in our hands, we can try to approach everyone as potentially repairable," he says. "No one should automatically be viewed as not being a repair candidate. Everyone should have an opportunity."

He says he often gives talks to cardiologists and cardiac surgeons throughout the world, trying to promote the concept and techniques of repair. While there is interest and curiosity, he says he also has met with some skepticism, as these surgical techniques are new and can take years to master. Some are simply resistant to change.

"It's an ongoing challenge to educate the community that aortic valves can be repaired," Woo says. "Either they have never heard of it or they've never seen it done effectively by a surgeon. Or they don't want to try it out until there is long-term durability data," which is not yet available.

He is also training the next generation of surgeons — people like Goldstone, now a resident in cardiac surgery at the University of Pennsylvania, who has been working with Woo over the past seven years both at Stanford and Penn learning these approaches.

"We are trying to train him and others at a very young age so they will carry on and further advance these complex reconstructive techniques," Woo says. "Through those whom you educate and train, you create a pathway for benefiting society for many decades down the road."

### HEALING HEALEY

As for Nathan Healey, he fully recovered from his marathon repair procedure after spending 10 days in the hospital. Woo implanted a pacemaker in his heart, as the rupture disrupted its natural rhythm. Healey was able to return to professional tennis and three years later went on to try his hand in the 2015 U.S. Open. He says he is likely one of the few players with a pacemaker to compete at that level.

In the fall of 2016, he moved with his family back to his native Australia, where he now coaches tennis, starting each session with a meditation. He also teaches yoga, surfs and competes in the occasional tennis tourna-

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*Stanford Medicine* is published four times a year by the Stanford University School of Medicine Office of Communication & Public Affairs as part of an ongoing program of public information and education.



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ment. He has the perspective on life that comes from being close to death, he says, trying to maintain a sense of balance and relishing every day.

Occasionally, he says, there is "this little fear that arises," the panic that his heart could fail again, but he is monitored regularly, and his doctors have assured him it's not likely to happen.

"I'm just incredibly grateful to be enjoying the life I'm living," he says. "A lot of fortunate pieces fell into place that night. I was lucky to get the surgeon and I was lucky to get the repair." **SM**

— Contact Ruthann Richter at [richter1@stanford.edu](mailto:richter1@stanford.edu)

# BAOBAB? WHO KNEW?

## FROM HUNTER-GATHERERS, CLUES TO DWINDLING GUT-BUG DIVERSITY

For more than 15 million years, humans have co-evolved with thousands of microbial species that take up residence in the intestine, earning their keep in many ways. They help us digest food components we're unable to break down by ourselves, chiefly dietary fiber. They manufacture vitamins and other health-enhancing molecules. They train our immune system and foster the maturation of cells in our gut. They guard our intestinal turf against the intrusion of competing microbial species, including pathogens.

Scientists who study these communities of microbes have noted that the species mix has changed over the centuries, becoming markedly less diverse. They had a hunch that the radical alteration in diet over the millennia has been a major factor in these changes. But how to test that hypothesis?

That's where members of a small group of hunter-gatherers inhabiting Tanzania's Rift Valley enter the story. This group, known as the Hadza, number just over 1,000 people, fewer than 200 of whom adhere to the traditional hunter-gatherer lifestyle, which includes a diet composed mainly of five items: meat, berries, baobab (a fruit), tubers and honey. While Western diets are pretty much the same throughout the year, the Hadza lifestyle doesn't include refrigerators and supermarkets. So the population's diet fluctuates according to the season, of which there are two in the Rift Valley: dry, when meat, baobab and tuber consumption play a relatively larger role; and wet, during which berries, tubers, honey and baobabs prevail. (Tubers and baobab are available year-round.)



Researchers studied the gut-microbial composition of members of the Hadza, a hunter-gatherer population in Tanzania.

A team of researchers led by Justin Sonnenburg, PhD, associate professor of microbiology and immunology at Stanford, collected 350 stool samples over a one-year period — a full seasonal cycle — from 188 Hadza people, and analyzed their microbiota.

“Surviving hunter-gatherer populations are the closest available proxy to a time machine we in the modern industrialized world can climb into to learn about the ways of our remote human ancestors,” says Sonnenburg, who is a senior author of the study, published Aug. 25 in *Science*.

“The 100 to 200 Hadza sticking to this routine will possibly lose it in a decade or two, maybe sooner. Some are using cellphones now. We wanted to take advantage of this rapidly closing window to explore our vanishing microbiota,” he says.

The research confirmed that the Hadza microbiota is more diverse than, and substantially different from, that of industrialized countries' urban-dwelling denizens.

Analysis of their stool samples also showed that fewer of a subset of microorganisms are present during the wet seasons, but the levels increase during the dry seasons when consumption of fiber-rich tubers peaks. It also shows the microorganisms that increase in the Hadza and other hunter-gatherer groups when more high-fiber foods are added are the same ones missing from the guts of most people in the industrialized world.

So, yes, though other factors could be at play — for instance our increasingly sedentary existence and the introduction of antibiotics — the change in diet seems to be a major factor in the reduced microbial diversity in the guts of those of us who are not hunter-gatherers. — BRUCE GOLDMAN

Stanford University  
School of Medicine  
Office of Communication and Public Affairs  
3172 Porter Drive  
Palo Alto, CA 94304

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# The ultimate smoothie

BABY MARSUPIALS NURSE ON HOPPED UP MILK

**Modern mothers, whether they be human or mouse, might be forgiven for envying marsupial mamas.** Rather than enduring a long pregnancy and the birth of a relatively well-developed — and comparatively large — baby, kangaroos, wallabies and their ilk blithely pop out offspring after pregnancies measured in days rather than months.

These tiny, almost formless creatures then make their own intrepid way up to the mother's pouch to nestle politely and nurse for sometimes as long as a year.

For decades, researchers assumed that this premature eviction from the womb left little or no role for the placenta, an organ that forms in the uterus of most mammalian mothers during their pregnancy. It links the mother's physiological processes with those of the fetus to support the many stages of fetal development. Recently, however, it has become apparent that marsupials do sport their own, rudimentary version of this important organ.

Now researchers at the Stanford University School of Medicine and the University of Melbourne in Australia have learned that female tammar wallabies produce proteins for later-stage fetal development in their mammary glands — a kind of handoff of the developmental baton from womb to teat that suits their unique, savanna-hopping lifestyle.



WALLABY MOMS PRODUCE PROTEINS FOR BABIES' LATER-STAGE FETAL GROWTH IN THEIR MAMMARY GLANDS.

"Although the placentas of humans, cows or mice are extraordinarily different from those of marsupials, the animals are fulfilling the same necessary functions in different ways," says Julie Baker, PhD, professor of genetics at Stanford.

Baker shares senior authorship of the study, which was published online Sept. 12 in *eLife*, with Marilyn Renfree, PhD, a professor of zoology at the University of Melbourne. The lead author is Stanford graduate student Michael Guernsey.

"Essentially, we're trying to understand how the placenta evolved in the first place," says Guernsey. "We're finding that we can begin to identify rudimentary placentas in other species as well, like lizards and fish. It will be really interesting to see whether, in this completely different evolutionary landscape, these functions are still conserved in ways that make sense for that animal."

— KRISTA CONGER

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