

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

Spring 2018

special report

SOUND WAVES
THE ART AND SCIENCE
OF HEARING

Lending an ear

The doctor-patient bond
needs nurturing

Noisy data

Researchers put sound and
acoustics to work

Antibiotic reboot

Fixing one drug's nasty side effect

Music as therapy

A conversation with opera singer
Renée Fleming

Smart tech

Improving how machines listen

Now hear this

Better, less costly treatments for
hearing loss coming soon

Healing deafness

The ability of birds to regrow inner
ear cells could be a clue

plus

#ILookLikeADoctor

A call for more
doctors with disabilities

3D science

Scientist's sculptures bring data to life



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TELL ME YOUR STORY

HEALING AND HELPING OTHERS BY SHARING EXPERIENCES

Best friends Margaret McCulloch and Jackie Fitzpatrick reminisce as if they're sitting on a porch sharing a bottle of rosé. But unlike typical conversations between the friends, this one is being recorded for the Stanford Storybank program and will be shared with the Stanford Health Care community. On this day, Esther Chyan, RN, a Stanford Cancer Center supportive care manager, is recording the conversation and ensuring it's clear. Bryanna Gallaway, director of the Service Excellence program at Stanford Health Care, stands by to facilitate. But the friends don't need guidance. "I clearly remember the day you told me there was a lump in your breast," McCulloch, 52, tells Fitzpatrick, 54, as the two sit in an improvised recording studio on the third floor of Stanford Cancer Center South Bay in San Jose.

When Fitzpatrick was diagnosed with cancer, McCulloch told her not to worry. But McCulloch now admits that "when I got the phone call that you were diagnosed with stage-4 breast cancer, my heart sank."



SHC is conducting the Storybank program in partnership with StoryCorps, a national organization whose mission is to capture, honor and preserve stories about human experiences through audio interviews. Each 40-minute conversation features two people — a patient and a family member, for example, or two SHC employees. If participants agree, the conversation will be archived within the U.S. Library of Congress and edited for SHC use.

The program is intended to allow patients and staff to share their experiences as well as learn, connect, heal and inspire. The stories "bring us back to why we're here, why we do what we do," says Alpa Vyas, vice president of patient experience for SHC. The Service Excellence team highlights a story a month on SoundCloud at <https://soundcloud.com/patient-experience>.

Before they start, Gallaway tells Fitzpatrick and McCulloch: "It's OK to cry; it's OK to laugh; it's OK to do anything you would normally do in a conversation."

In the recording session, the friends, who met 12 years ago when their children were in kindergarten, talk about how Fitzpatrick's cancer, diagnosed six years ago, affects their lives and friendship.

"How do you distract your mind, not to think about cancer 24/7?" McCulloch asks.

"I don't dwell on the negative stuff," Fitzpatrick says. "I admire that about you," McCulloch responds.

"The one thing that cancer has given me is a clear, concise view on my family and what's important to me," Fitzpatrick continues. "I made amends with people I needed to make amends with. It's a blessing. It's been a difficult journey, but it's kind of worth it."

They laugh about how Fitzpatrick's hair grew back white after a round of chemotherapy and she looked like Annie Lennox. "I kind of had fun with it," Fitzpatrick says.

Turning serious, she asks McCulloch, "What's it like for you? I sometimes think it's harder for the people not going through it." McCulloch confesses, "Sometimes I think that I'm weak. I want to make you better, but I can't."

The friends say it was cathartic to share their story, and Fitzpatrick says she hopes the Storybank program can help others. "I really want to provide hope to people in the same situation." — MANDY ERICKSON

Contact cicare@stanfordhealthcare.org to participate in Stanford Storybank.

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

SPECIAL REPORT

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letter from the dean



A heartbeat.

This most fundamental of sounds carries great meaning and deep-seated emotion. From it comes the most basic sign of life. Through its rhythm, sound assumes a foundational role in our development.

A baby's cry brings her father's soothing touch.

A 30-something turns up the radio, transported back to a high school dance on the notes of a song.

A grandmother smiles wide at the sound of an old friend's voice on the phone.

Listening, whether literally with our ears or metaphorically with understanding, is at the heart of every relationship. It is also the lifeblood of any strong physician-patient rapport.

Why? Because while you can share a passing glance and experience a brief touch, listening requires us to slow down, maybe even to stop. To do it well, what we call active listening, requires giving someone our full attention.

Listening is fundamental to so much of who we are, yet exactly how we process sound and how it affects us emotionally and physically remain unknown.

This fascinating issue of *Stanford Medicine* dives into that mystery.

I marveled at its four examples of how sound is being used in innovative research: tuning in to brain waves to “hear” neurological health, tracking mosquitoes through their whines, harnessing the power of ultrasound and using acoustic waves to study heart cells themselves.

One article demonstrates how artificial intelligence and machine learning can help us listen our way to better, more efficient health care and provides a sampler of the intelligent listening technologies emerging from Stanford, including a mental health chatbot and a social media data miner for drug side effects.

The magazine also explores the deep connection between empathy, listening and the doctor-patient relationship, a subject promoted by Stanford's Presence program, which recognizes that our instinctual need to care for those who suffer is one of the most poignant of human experiences.

Another story warns of a growing threat. For all its importance, we neglect our hearing, a fact I know well from my years treating patients. But because of the research of my colleagues in neurotology, we might soon be able to get ahead of this growing health crisis — and maybe even reverse hearing loss.

Finally, the incomparable soprano Renée Fleming discusses an initiative called Sound Health Music and the Mind that explores how music can be harnessed to improve health and well-being. She describes her experience singing while undergoing an fMRI scan, something I discussed with her when she was at Stanford Medicine recently to talk about this collaboration between the John F. Kennedy Center for the Performing Arts and the National Institutes of Health.

Listening is intrinsic to human relationships. Done well, it's a powerful talent, and when freely given, a momentous gift.

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

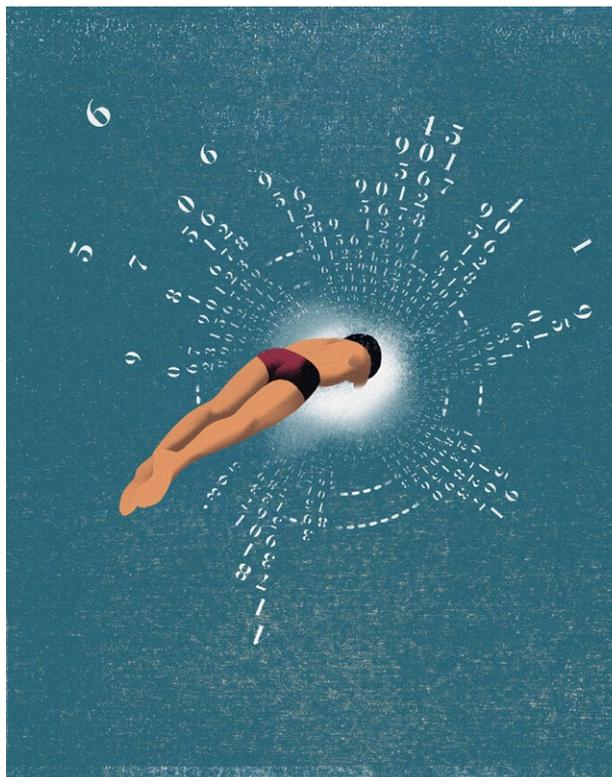
Math brain

ATTITUDE IS EVERYTHING — at least if you want to be great at math. Researchers for the first time have found the brain pathway that helps explain why elementary school children with positive attitudes about math are better at it.

“Based on our data, the unique contribution of positive attitude to math achievement is as large as the contribution from IQ,” says Lang Chen, PhD, a postdoctoral scholar in psychiatry and behavioral sciences.

Chen is the lead author of a study published Jan. 24 in *Psychological Science* that says a positive attitude about math links to better function of the hippocampus, an important memory center in the brain, while working on arithmetic problems.

Researchers previously hypothesized that the brain’s reward centers might drive the link between attitude and achievement — perhaps children with better attitudes were better at math because they



found it more rewarding or motivating.

“Instead, we saw that if you have a strong interest and self-perceived ability in math, it results in enhanced memory and more efficient engagement of the brain’s problem-solving capacities,” says the study’s senior author, Vinod Menon, PhD, professor of psychiatry and behavioral sciences.

Children with poor attitudes toward math rarely performed well in the subject. “A positive attitude opens the door for children to do well but does not guarantee that they will; that depends on other factors as well,” Chen says.

The liver can fully regenerate from as little as 25% of its original mass — but how? Learn at <https://stan.md/2v0jUnn>.

Military moms

Nearly 12 percent of women who gave birth shortly after returning from military deployment had preterm deliveries, compared with 6.1 percent of other active-duty servicewomen, a Stanford study showed.

Jonathan Shaw, MD, clinical assistant professor of medicine and lead author of the study, used military records to track 12,877 births from 2011 to 2014. Because being pregnant during deployment appeared to raise the risk of preterm birth, he suggests that women could be advised: “It’s a pretty stressful time; consider returning home and settling in for a few months before you add to your family.”

The study was published March 1 in the *American Journal of Epidemiology*.

Dancing DNA

WHILE DEVELOPING A NEW TECHNIQUE FOR labeling individual stretches of DNA, scientists discovered that DNA flails around during transcription, the process in which instructions encoded in genes are used to make RNA.

The technique, termed CARGO, is a variation of the CRISPR/Cas9 gene-editing tool used to seek out and replace specific DNA sequences in the genome with other DNA sequences. CARGO can precisely tag any stretch of DNA with fluorescent molecules to track its three-dimensional location and movements, according to a study published Jan. 24 in *Science*.

Researchers used CARGO, which they say could answer many questions about the genome or gene expression, to learn that the act of transcription agitates DNA strands, increasing the ability to bring distant regions of the genome together.

DNA that wiggles during transcription was entirely unexpected, says senior author Joanna Wysocka, PhD, professor of developmental biology and of chemical and systems biology.

"It's just one example of what we and others can now learn by using CARGO to label specific DNA regions."

Weighing in

WONDERING WHETHER A LOW-CARB OR LOW-FAT DIET IS BETTER FOR LOSING WEIGHT? A recent Stanford study suggests that people, on average, lose about same amount of weight on either one. The study also notes that you can't predict the answer by looking at insulin levels or certain gene sequences that affect carbohydrate or fat metabolism.

The study, published Feb. 20 in *JAMA*, zeroed in on genetics and insulin to discover whether these factors encourage an individual's body to favor one over the other.

Christopher Gardner, PhD, professor of medicine and the lead author, launched the study with 609 adults between the ages of 18 and 50, though only 481 finished. About half were men and half were women. All of them had their genome sequenced so scientists could look for patterns associated with producing proteins that modify carbohydrate or fat metabolism. They also took baseline insulin tests to measure output.

By the end of the yearlong study, weight loss averaged 13 pounds per person — some lost up to 60 pounds and some gained close to 15 or 20 — and Gardner found no associations between the genotype patterns or baseline insulin levels and a propensity to succeed on either diet.

Still, the study did change habits. "On both sides, we heard from people who had lost the most weight that we had helped them change their relationship to food, and that now they were more thoughtful about how they ate," says Gardner.



Invading tumors

AN EXPERIMENTAL CANCER treatment tested in mice eliminated all traces of the disease, according to a study published Jan. 31 in *Science Translational Medicine*.

The researchers believe the method, a way to rev up the immune system's T cells, could be a rapid and relatively inexpensive cancer therapy unlikely to cause the adverse side effects seen with bodywide immune stimulation.

T cells need revving because tumors often suppress their cancer-fighting activity. The method overcomes this by injecting two immune-stimulating agents into a tumor. Activated T cells then leave the original tumor and destroy others.

"When we use these two agents together, we see the elimination of tumors all over the body," says Ronald Levy, MD, professor of oncology and the study's senior author.

In the study, 87 of 90 mice were cured. Cancer recurred in the other three, but tumors regressed again after a second treatment.

Researchers plan a small study of the method's safety in people with non-Hodgkin lymphoma. For info, visit <http://med.stanford.edu/cancer/trials/vaccine.html>.

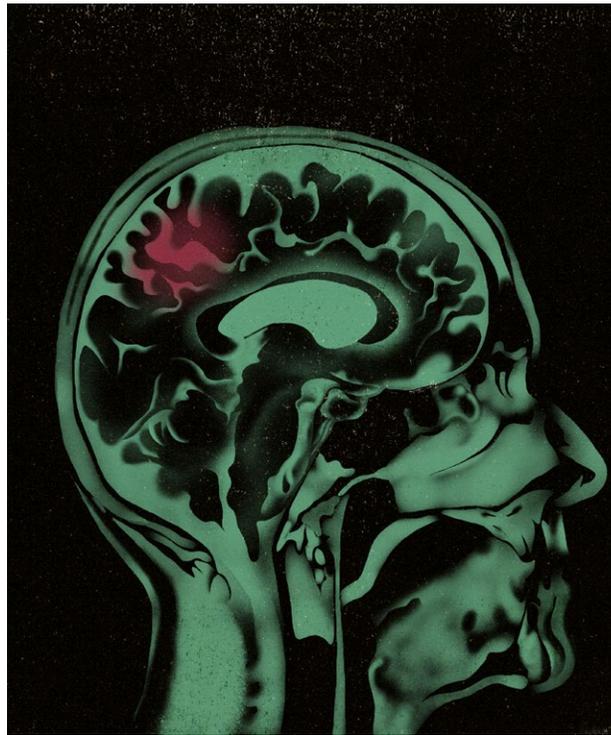
Before you go

IF YOU HAVE A BUCKET LIST, you might want to give a copy to your doctor. VJ Periyakoil, MD, clinical associate professor of medicine, says doing so provides a chance to discuss your care goals, especially if you have a chronic or terminal illness.

"Patients don't see the relevance of an advance directive. They do see the relevance of a bucket list as a way to help them plan ahead for what matters most in their lives," says Periyakoil, senior author of a study published Feb. 8 in the *Journal of Palliative Medicine*.

In the study, 91 percent of 3,056 people surveyed say they have a list of things they want to do before they die, including such things as traveling, running a marathon, skydiving or reaching a milestone birthday.

'I am literally standing on this Earth as a wife and mother because of that procedure.'



Resetting the stroke clock

WHEN CINDI DODD'S HUSBAND awoke her at 5 a.m. one day last year, something was wrong. "I knew what I was trying to say in my mind, but it had nothing to do with the sounds that were coming out of my mouth," Dodd, 47, says.

She had suffered a massive ischemic stroke. Now, she credits brain-imaging software developed by Stanford researchers with saving her life and preventing permanent disabilities.

At the time, treatment to remove clots was considered helpful for only six hours after a stroke. It wouldn't have been an option for Dodd because the time of her stroke was unknown. But the software, which assesses salvageable brain tissue, indicated that a thrombectomy, a clot-removal procedure, could help her.

"I am literally standing on this Earth as a wife and a mother because of that procedure," says Dodd.

A 182-patient trial of the software, funded by the National Institutes of Health and led by Stanford researchers, showed that the procedure was beneficial for up to 16 hours after a stroke.

"Nearly half of all patients treated between six and 16 hours after the onset of their symptoms were largely spared from the consequences of their stroke," says the trial's principal investigator Gregory Albers, MD, professor of neurology and neurological science and director of the Stanford Stroke Center.

The trial results, published Jan. 24 in *The New England Journal of Medicine*, were key to a decision by the American Heart Association and American Stroke Association to extend the treatment window to 24 hours.

Iron block

Transplanted lung tissue with high iron levels is more vulnerable to infection caused by a common mold called *Aspergillus fumigatus*, according to new research in mice and humans.

About a third of lung transplant patients get the potentially fatal infection. "Iron is like fertilizer for the *Aspergillus*," says Mark Nicolls, MD, professor of pulmonary and critical care medicine and senior author of the study published Feb. 21 in *Science Translational Medicine*.

Lead author Joe Hsu, MD, assistant professor of medicine, is studying a method for starving *Aspergillus* of iron rather than killing it with antibiotics. Nicolls is an inventor on a patent for a chemical solution that captures excess iron and could be applied like a paint during surgery, inhaled into the lungs or injected intravenously.

NOW

HEAR

THIS

LISTENING REALLY MATTERS

Listening is something
we often do without thinking, but it's not
something to be taken for granted.

For a physician, listening to patients' histories, concerns and goals is central to the craft, yet time to really tune in has become a precious commodity. For a person whose hearing is failing, the loss represents dwindling pleasures, connections and independence. The change can lead to depression and raises the risk of other health problems.

Helen Keller, though both blind and deaf, identified deafness as the worse misfortune: "For it means the loss of the most vital stimulus — the sound of the voice that brings language, sets thoughts astir, and keeps us in the intellectual company of man."

So, in this issue of *Stanford Medicine*, we seriously consider listening as well as the kindred topics of hearing, sound and simply paying attention. Read on to learn about efforts to hone the communication skills that are at the heart of health care, reasons to expect a revolution in hearing loss treatments, computer programs that listen in ways humans can't — and more.

ILLUSTRATION BY RICH TU



ARE YOU LISTENING?

MODERN MEDICINE
CHALLENGES
THE CRUCIAL BOND BETWEEN
DOCTORS AND
PATIENTS

Kimberly Allison, MD, was 33

when her diagnosis came. She was a couple weeks into a job directing the breast cancer pathology lab at the University of Washington Medical Center and happily settling into a new routine with her husband, a preschool daughter and an infant son.

The discovery that she had the disease she devotes her career to studying was “like Alice in Wonderland, falling down the rabbit hole.”

She couldn’t protect herself from what the scientist in her knew: Young women tend to get more deadly forms of cancer. And her cancer was ugly and big, likely having spread, undetected, during her pregnancy and breastfeeding.

Allison, now a professor of pathology at Stanford’s School of Medicine, recalls her deep depression after the diagnosis 10 years ago, when her mind went to the

BY PATRICIA HANNON

PHOTOGRAPH BY MAX AGUILERA-HELLWEG

A CONVERSATION WITH her oncology team helped Kimberly Allison, right, embrace her treatment plan after a devastating diagnosis.



“darkest places” as she scoured the internet for answers.

“Every study I looked up had a horrible outcome. I thought this was going to be a death sentence for me,” she says. “What if you only have two years left? You go there right away.” What should she do with that time? Sadness about her children overwhelmed her. Should she quit work and spend her time with them and her husband? Should she do something soul-fulfilling like writing or painting? Or keep working in a career she loves?

She wouldn’t be able to settle those thoughts until she saw her oncology team.

At the first meeting with her surgeon and two oncologists, Allison willed emotion away. She didn’t want to “be a total mess” in front of the physicians gathered around the conference room table with her and her husband. She wanted her colleagues to see her as professional and still capable of doing her job.

They discussed the characteristics of her cancer and her treatment options in a matter-of-fact way and created a plan: six months of chemotherapy, followed by surgery, then radiation. They could start right away.

But Allison was uneasy. “OK, but I’ve seen the pathology,” she told the team. “This looks really bad to me.” That’s when her surgeon, Kristine Calhoun, MD, saw through Allison’s tough facade to the fear she was struggling to keep at bay. Calhoun told her: “I know you’ve looked up your prognosis. But there are new, targeted therapies that are changing that outcome. That data is so new it’s not in the older papers about pregnancy-associated cancers.

“This is a new ballgame,” Calhoun said. “We’re talking about seeing the grandkids.”

Allison finally had hope: “That basically reset me like, ‘OK, I’m not dying. I’m not dying right now.’”

Calhoun, who is still at the University of Washington School of Medicine, says there’s a delicate balance in giving patients hope without giving them false hope, but it was important that Allison see a positive path forward. “People who lose hope kind of will themselves into a certain pathway,” she says. Though it was sometimes difficult to treat a friend, Calhoun says she learned a lot from how Allison handled the experience. “It taught me to have even more empathy,” she says. “It helped



HAVING EMPATHY is at the heart of medicine, says Stanford School of Medicine Dean Lloyd Minor.

me learn to not just look at patients as patients but as people, and to see that it really does change their story.”

The connection between Allison and Calhoun, which grew stronger as Allison’s treatment progressed, is what Stanford physician and author Abraham Verghese, MD, calls the “most poignant of human experiences” — one of suffering and the care of people who are suffering.

“The relationship between a care provider and a patient is vitally important in determining the health and well-being of the patient and the outcome of treatments,” says School of Medicine Dean Lloyd Minor, MD.

He notes that, historically, the most a physician could do for suffering patients was to offer comfort by being an empathetic and understanding listener.

A relatively recent explosion in biomedical knowledge and therapeutic options changed that and vastly improved care. But he says it also created a “separation between the science of medicine and the humanism and compassion of medicine” that must be addressed to nurture the ability of physicians to better understand and treat their patients.

“Each patient comes with a different history, with a different social, cultural and behavioral background,” says Minor. “Those factors are going to play heavily in determining the effectiveness of whatever scientifically based therapeutics you seek to offer.”

LISTENING IS CRUCIAL TO GOOD HEALTH CARE

CLINICIANS ACROSS THE BOARD SAY THE CURRENT CLIMATE OF medicine cuts into the time they can spend really listening to patients, which makes it difficult to form meaningful connections, says Donna Zulman, MD, assistant professor of medicine and co-director of Stanford Presence 5, an initiative to change clinical encounters to improve overall health care. The initiative was launched by the Stanford Presence Center — founded in 2015 by Verghese to develop methods of tearing down communication barriers created by technology.

Not listening can have negative consequences downstream, such as misdiagnosis, unnecessary or unwanted treat-

TIMOTHY ARCHIBALD

ment, patients not following through, fragmented patient care and physician burnout, Zulman says.

She is one of many people — at Stanford and elsewhere — who are working to enhance the doctor-patient relationship by creating communication skills training for clinicians; addressing physician burnout; and developing ideas for better ways to manage care, design exam rooms and improve health record interfaces.

Zulman points to two main time-robbing culprits: reimbursement models that have resulted in appointment times across the nation being set at about 15 minutes; and electronic health records that have clinicians spending more time outside of the appointments entering, reviewing and sharing patient information.

Such demands on physicians take them far from the reasons they got into medicine.

Kelley Skeff, MD, PhD, professor of medicine, who co-directs the Stanford Faculty Development Center for Medical Teachers, says doctors came to the field “to learn and apply science for the benefit of patients.”

“But their connections to science and to the patient are commonly impeded by the requirements of the system,” he says. “And those who are the most empathetic may, in fact, burn out faster as their self-care is neglected.

“We’re asking them to do the relatively superhuman tasks of keeping humanness and empathy together for others. They’re drawn to respond to the needs of both the health care system and the patient, but their own refueling process isn’t always happening.”

Physician burnout is at an all-time high; 54 percent of physicians across the nation reported having at least one symptom of burnout, according to national research overseen in 2014 by Tait Shanafelt, MD, the chief wellness officer and director of the Stanford Medicine WellMD Center. That was up from 46 percent in 2011. A physician wellness survey the center conducted at Stanford in 2016 showed that 34 percent of physicians surveyed that year reported having at least one burnout symptom. That was up from 25 percent in 2013.

Caring for the caregiver has been neglected for years, says Minor, but change is coming. “We have to get real about this,” he says. “I think we’re starting to recognize that our physical and mental well-being are just as important as our knowledge base and technical skills when it comes to being effective physicians.”

One key challenge, says Minor, is to better integrate technology with medicine. For example, it’s important that electronic health records be better designed and

easier to use so health care professionals and patients can access and share the information — and communicate about it — in real time.

“The care-delivery experience should not be driven and determined by the technology, it should be enabled by the technology. Listening to patients and being empathetic with patients should be the priority,” he says.

IMPROVING HOW WE TALK TO EACH OTHER

GOOD COMMUNICATION, Zulman says, starts with clinicians really absorbing what patients say — about themselves, their pain, values, challenges and care goals — and being empathetic.

“Now, because of pervasive technology and other distractions in the clinical setting, we’re having to be more explicit about taking time and taking actions that will help us have meaningful interactions with patients,” she says.

Still, superb communication skills don’t come naturally to everyone, even the most experienced clinicians, says Stephanie Harman, MD, clinical associate professor of medicine. Like other aspects of medicine, being a good communicator takes practice.

“Learning how to build strong patient relationships is equally as important in medicine as learning technical or procedural skills,” says Harman, a master facilitator for Advancing Communication Excellence at Stanford, a workshop designed to help clinicians enhance communication skills that are “really at the heart of how we care for patients and their families.”

Workshop participants role-play patient interactions so patient priorities are at the center of every discussion. A total of 310 clinicians have participated in the program as of April 1 and 310 more are registered to participate between now and August. Harman says they’re encouraged to suspend the impulse to rush through patient conversations and instead listen, so that amid the “all-consuming fracas” of information and tasks they manage, clinicians can “answer the most important question in the world: What does the patient need?”

To gain a better understanding of effective doctor-patient dynamics, Presence 5 researchers are sitting in on patient interactions with primary care providers at Stanford and in primary care clinics in the Alameda Health System, Ravenswood Family Health Center in East Palo Alto and the Veterans Affairs Palo Alto Health Care System.

If patients agree, researchers use video or audio devices to record the encounters. The data also will include survey

A RELATIONSHIP BUILT ON TRUST

ONE PATIENT
SAYS A STRONG
RAPPORT
WITH HER DOCTOR WAS
CRUCIAL IN
FINDING SUCCESS

STACY SERBER, PHD, A STANFORD Health Care clinical nurse specialist, struggled with being overweight for much of her life, but everything changed when she started seeing Megan Mahoney, MD, clinical professor of medicine.

To Serber, finally finding success in losing weight is the result of how Mahoney approaches their relationship and Serber's wellness. "It's more than, 'What are your medical problems?'" She listens and she meets me where I am," Serber says. "I'm the kind of person who can dig in my heels. But she doesn't tell me what to do. She doesn't browbeat me. She takes time with me and I never feel rushed when I'm with her."

Mahoney, who is the section chief of general primary care in the Division of Primary Care and Population Health, recommended during their first appointment together that Serber see a nutritionist to help her lose weight, but Serber declined. Mahoney gently pushed back: "It's something I would like you to do. If you're not comfortable, we'll leave it at that. But would you be comfortable revisiting this in six months?"

Serber agreed. And when nothing changed in six months, she agreed to see the nutritionist and enrolled in Stanford's Omada Health program, which helps people who are at risk for diabetes and heart failure because of weight make long-term lifestyle changes.

Serber lost 54 pounds in a year. Along the way, Mahoney cheered on



HAVING A TRUSTING RELATIONSHIP with her physician, Megan Mahoney, right, was a catalyst for Stacy Serber, left, to make lasting health changes.

Serber's successes and focused on Serber's goals and challenges.

Mahoney says she finds immense gratification in having that kind of experience with her patients. "That's why I became a doctor." She also wants patients to know "they're walking this journey with somebody."

"I want people to leave feeling better, not from their symptoms, but because they had a connected experience with someone they could trust — that they felt like they were heard, that we came up with a plan together, and that they were participants in develop-

ing the plan," Mahoney says.

For some patients, it takes more digging to get there. If, for instance, a 30-year-old, fit man is having chest pains and his biggest fear is that it's a heart attack, she can't just do an EKG, say, "No, you aren't," and send him away. She has to address "the question behind the question." Maybe his best friend just had a heart attack.

"If you aren't addressing the fears, concerns and expectations of the patient when they come in for the first visit, they'll come back for another visit," Mahoney says. — PATRICIA HANNON

MAX AGUILERA-HELLWEG

feedback from the patients and physicians involved in the approximately 40 visits that are being observed. Researchers will eventually synthesize the information to help establish best practices for interacting with patients.

They're watching, Zulman says, for moments when patients reveal valuable information about themselves, their symptoms or their social histories that can inform clinical decisions. "What happens in the minutes preceding that? What did the doctor do or say, how were they positioned, that helped the patient open up in that way?"

LEARNING WHAT PATIENTS NEED MOST

JOHAN KUGLER, MD, a clinical associate professor of medicine who launched Stanford Medicine 25 with Verghese nine years ago to promote bedside exam skills, emphasizes the importance of those personal interactions for both diagnostics and for building trust between the physician and patient.

When a trainee seeks Kugler's advice about a patient, "My first answer is, 'We can't make that decision now. We need to see the patient first.'"

"You learn so much stuff that's between the lines. How much distress are they really in? Can they really not breathe? Can they talk to me in full sentences? How weak are they? I'm really trying to get a sense of the person," he says. "That's when the decision-making just gels a lot better. To me, so much of it is that initial laying eyes on someone."

Verghese, the Linda R. Meier and John F. Lane Provostial Professor and a leading advocate for returning to the "timeless human-to-human ritual" of bedside exams, says he takes note of what's in a hospital room before even approaching a patient.

"They're totally out of their context," he says. "So anything that they've brought from the outside world is enormously helpful." One person might be in shackles, another might be reading a book or Bible. Or a hospital room might be filled with greeting cards and family photos. Such observations can reveal a lot about people, he says, including values, cultural backgrounds, cognitive abilities and support networks.

"So often we walk into a room and, because of what the chart says or what we notice, within moments we know what's going on," he says. "But the patient doesn't know what we know. If you jump in and say, 'Well, I know what's going on,' it just seems so rude. And they wonder, 'What do you already know? I haven't really finished telling you.'"

Letting them tell their stories in a way that shows respect for them as individuals also invites patients to be partners in their care.

When Allison was fighting stage-3 HER2-positive breast

cancer, she wanted to keep working and keep normal routines for her kids. During the first six months, she had chemotherapy once a week. In between, she diagnosed patients and presented pathology to physician groups working on other cases. The schedule, she says, helped her "feel balanced and like I was still engaged in my life. And I found it actually quite nice to go to work and not be focusing on illness all day at home."

But she also needed emotional support. That, she says, especially came from the wider team of oncology nurses and staff. Memories of their kindness still evoke tears of gratitude. "You're sitting there for hours, sometimes for a whole day, and those are the people who come and sit next to you, hold your hand, bring you a warm blanket or food, and really get to know you as a person," she says.

Comfort also came from conversations with a hospital chaplain who visited the infusion ward. "Just having somebody to talk to who could bring up some big questions for you to ask yourself, about values and to reflect, was a growing experience without even going through cancer treatment," Allison says. "It was like therapy."

Now she meets with patients who want their pathology lab results explained, which is unusual for a pathologist, and speaks with patient groups, encouraging patients to do what they can, such as get a second opinion or learn more about treatments, so they trust and are comfortable with their care team and treatment plans.

She also speaks to physicians, challenging them to see patients quickly after a diagnosis — because "the worst time is that fearful time" of waiting — and to treat them as individuals.

"The hope you gave or the care you gave where you made it personal makes a huge difference," she tells them. "I knew that I was getting the best treatments. But it was the personal interaction and support that I got as a patient that made a difference for me every day."

FINDING A MODEL THAT WORKS

MINOR, WHO TAUGHT AN UNDERGRADUATE SEMINAR THIS winter on literature, medicine and empathy, says the sense that the whole team is on your side is crucial for a patient's motivation and healing, and contributes greatly to the wellness of care providers. "Being a physician is a calling," he says, "partly because of the enormous privilege of interacting with people in a way that establishes deep personal relationships that are unique to health care."

Alan Glaseroff, MD, adjunct professor of medicine, is working with Arnold Milstein, MD, professor of medicine

C O N T I N U E S O N P A G E 3 6

SOUND

RESEARCH

SCIENTIFIC
INNOVATIONS
HARNESS
NOISE
AND
ACOUSTICS
FOR
HEALING

[From the original stethoscope.](#)

invented more than 200 years ago, to the fleeting chirp of gravitational waves, sound has reverberated throughout the history of technological and scientific advances. Today, the role of sound in science extends beyond the range of audible frequencies: Ultrasonic and other silent acoustic waves have made their way into researchers' repertoire, helping them push the boundaries of conventional medicine and research.

In examples from four Stanford labs, scientists are investigating the full spectrum, harnessing the nuances of noise and the power of acoustics to generate inventive, if not unexpected, technologies that show just how potent the combination of sound and science can be.

BY HANAE ARMITAGE

ILLUSTRATION BY DAVID PLUNKERT



TURNING THE IRKSOME INTO THE ADVANTAGE

Nothing incites irritation in quite the same way as a lurking mosquito. But its high-pitched drone may actually help curb spikes in mosquito populations and, more importantly, the diseases that they pass on to humans. This, at least, is the premise behind Manu Prakash's newly launched app, Abuzz.

Prakash, PhD, assistant professor of bioengineering, created Abuzz to digitally identify and tag mosquito species based on their hums. His vision: build a "soundscape" that maps the global whereabouts of these voracious vectors and provide details about the diseases they can carry — Zika, malaria, dengue and the like. It may seem lofty, but Prakash asserts that all he needs is an avid user base with access to cellphones ("dumb" phones like a flip phone make the cut).

"Our goal is to put the data in the hands of locals and public health organizations who are focused on mosquito-disease elimination," Prakash says. "We want this to provide details of mosquito ecology — species, associated diseases, the location of the recording — so that it can be a worldwide

hinder populations by releasing genetically modified mosquitoes could use the information to more precisely target regions and species. (Releasing an army of mosquitoes into the ether may sound rather vile, but gene modifications in these mosquitoes make their offspring unviable, helping to curtail a climbing population.)

"What's beautiful about Abuzz is it's not just limited to mosquitoes," says Prakash. "Right now, we're looking into whether we can use this method to identify sick versus healthy honeybees." They don't have the answer, but as health of honeybees in the United States continues to decline, Prakash and his team hope that their platform can help reveal the biology behind more than one flying insect.

ACOUSTIC CHOREOGRAPHY

Heart cells are among the most densely packed in the body — about 100 million fit into a space the size of a sugar cube. The compact structure crams the cells so close together that they can communicate with one another and beat as one lump. For tissue engineers, however, it poses a tricky hurdle: Pack

'LOCALS COULD LOOK IN THEIR

awareness and alert system for disease-carrying mosquitoes."

Naturally, populating such a map will take time, and a lot of users. So how does one collect that much data from far-flung corners of the globe? Recruitment and a simple training session, Prakash says, that consists of four basic steps: venture out, creep up to a mosquito (or let it creep up to you), record its pitchy hum and send the data to Abuzz for analysis.

Abuzz — the Shazam app of the insect world — uses software to determine if the recorded noise is really a mosquito, not a house fly, distant jet or other imposter. Then, it compares the recording with a database of different mosquito buzzes and tries to find a match. This is possible because every mosquito species emits a unique sound, generated by the flutter of its wings.

Ideally, knowing the geographic regions where specific mosquito species are recorded can help battle unwanted multiplication. "Locals could look in their neighborhood for likely mosquito-spawning areas and remove the larvae," Prakash suggests. Or, on a larger scale, agencies that try to

the cells too tightly and some won't get proper nutrients; too loosely and they can't coordinate a beat.

Cardiologist Sean Wu, MD, PhD, had been probing the problem when he met Utkan Demirci, PhD, an acoustic bioengineer and professor of radiology. "Utkan brought up this idea that we could use acoustics to pack the cells very densely and still maintain an ability to control and tune their organization — and we got really excited," says Wu, associate professor of medicine.

Demirci's idea exploits a type of acoustic signal that creates Faraday waves, which result from a physical perturbation at the interface of liquid and air (if you've ever flown in a turbulent plane with a beverage, you've witnessed Faraday waves in your cup). The waves cause ripples in the liquid, and anything floating in the liquid sloshes around too.

"You can trigger those ripples on the microscale," explains Demirci. "Like when the tides of the ocean sweep a sunken ship's treasures to shore — we're sort of doing the same thing with heart cells." The big difference, however, is that

Demirci and Wu can control the “swell” by tuning a knob that changes the waves.

Wu and Demirci can then shepherd the heart cells into nearly any pattern they want. “You can make triangles, hexagonal shapes, circles, lines — you can even make a little human shape,” Demirci says.

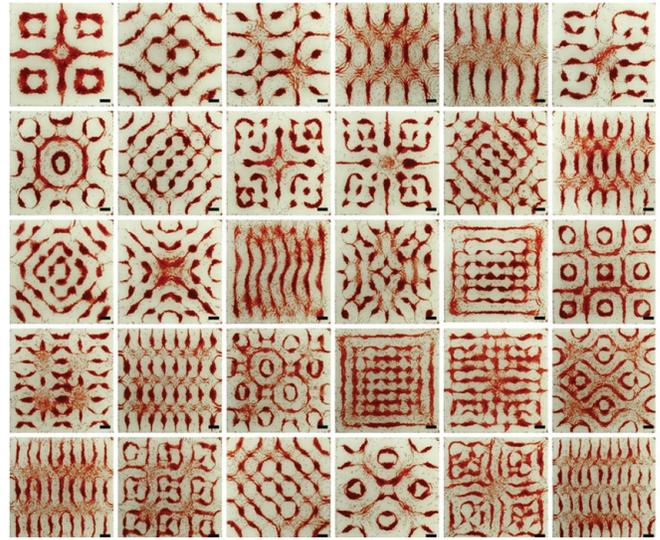
“And,” Wu adds, “if you don’t like the pattern, for whatever reason, you can change it, literally, within five or six seconds. You change the frequency and amplitude, and the cells move into a new spot right in front of your eyes.”

Unlike other tissue engineering tactics, acoustics position the heart cells in a tight configuration that closely resembles natural cardiac tissue, turning the resulting, beating blob into something valuable for medicine.

Wu and Demirci think acoustic engineering could help foster more realistic cardiac disease modeling and drug screening. More distantly, but still on the horizon, the pair even see their generated tissue as an option for heart patches in patients who have weak cardiac walls or have damage from a heart attack.

something that Parvizi has dubbed the brain stethoscope.

The instrument, which is noninvasive and looks like a sweatband, straps onto a person’s head and listens to the



UTKAN DEMIRCI AND SEAN WU use acoustics to manipulate heart cells into intricate patterns. A simple change in frequency and amplitude puts the cells in motion, guides them to a new position and holds them in place. Watch the cells move at <https://stan.md/2JliP65>.

NEIGHBORHOOD FOR LIKELY MOSQUITO-SPAWNING AREAS.

Next, Demirci and Wu say that they plan to add vascularization — conduits that carry blood and oxygen to various parts of an organ — to make their generated heart tissue even more realistic.

A SYMPHONY IN THE BRAIN

While listening to a string quartet play over recordings of plasma waves captured in outer space and converted into sound, neurologist Josef Parvizi, MD, PhD, dreamed up a symphony of his own. If you can turn signals from space into sound, perhaps you could turn brain waves into sound too, he thought.

So Parvizi sent an out-of-the-blue email to Christopher Chafe, a composer with expertise in converting atypical data sets into music, and explained his vision. Parvizi, professor of neurology, describes what happened next: “A crazy music professor and a crazy neurologist decided to collaborate on a strange idea.” Chafe is the director of Stanford’s Center for Computer Research in Music and Acoustics.

After several years of refining, the idea developed into

brain’s electrical signals. With a push of a button, those signals are converted to sound that streams from a small speaker connected to the band. The thought is that doctors can “hear” the tone of the brain — particularly if there is a seizure.

“Imagine that you open a hotel room window and the entire town is chanting exactly the same thing,” says Parvizi. “You may not know exactly what’s happening, but you know it’s not normal. It’s the same idea with the brain; you don’t want signals to be too synchronous. If they are, the brain is having a seizure.” It turns out, the audible difference between a seizing brain and a normal brain is quite distinct; almost anyone can hear it.

Of course, Parvizi acknowledges, if someone is convulsing and shaking, you don’t need a stethoscope to tell you they’re having a seizure. “But there’s such a thing as ‘non-convulsive subclinical seizures’ and those don’t have the obvious physical symptoms.”

But they still have some subtle symptoms. Someone having one of these silent storms might appear disoriented and

C O N T I N U E S O N P A G E 3 7

A TOXIC LIFESAVER, RECONSTRUCTED

FIXING
A
WIDELY
USED
ANTIBIOTIC'S
TENDENCY
TO
CAUSE
HEARING
LOSS

Seated at his desk in the

Edwards Building on the Stanford campus, Tony Ricci, PhD, professor of otolaryngology and a renowned biophysicist, looks more like a mechanic than a scientist. Routinely dressed in jeans and sneakers with a well-worn New York Yankees cap, Ricci has spent his entire career under hoods, but the kind you find in research labs where he tinkers around with high-tech tools.

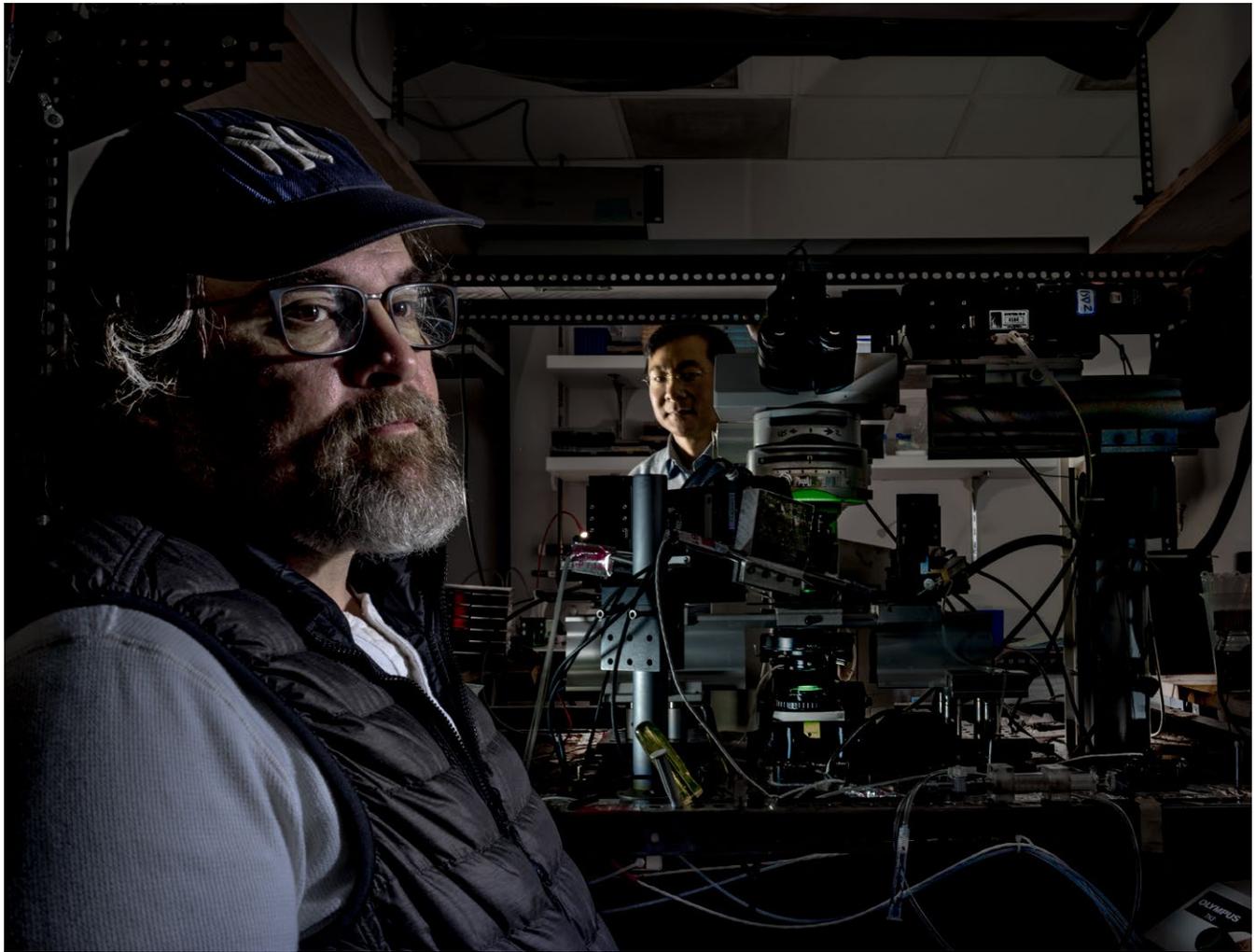
Ricci has studied the molecular workings of the inner ear in labs from Cleveland to New Orleans and finally, pushed out by Hurricane Katrina, to Stanford in 2006. It was while working in his New Orleans lab that Ricci experienced an “aha” moment that sent him down a new path — drug design. Ricci, a confirmed lab rat, now working in partnership with Alan Cheng, MD, a physician-scientist at Stanford, is intent on building a safer version of a commonly used class of antibiotic that can cause deafness.

“I never thought I’d be doing something like this,” says Ricci, a familiar sentiment for the Bronx-born son of a taxi driver who once thought school was a waste of time. He grins, pushing back his Yankees cap, and adds, “What do I know about making a drug?”

Aminoglycosides, one of the most commonly prescribed classes of antibiotics in the world, are used to treat a broad spectrum of bacterial infections from peritonitis to sepsis to pneumonia.

BY TRACIE WHITE

PHOTOGRAPH BY MAX AGUILERA-HELLWEG



They're used to treat cystic fibrosis and tuberculosis patients, low birthweight babies and many others with an infection of unknown origin. While the drugs save countless lives, they also cause hearing loss in about 20 percent of the patients who take them. Because cystic fibrosis causes chronic lung infections, patients with the condition need repeated doses and are particularly at risk: Up to 56 percent of them suffer from hearing loss.

Developed in the 1940s, the drugs' popularity has continued to grow, despite the introduction of newer, alternative antibiotics. Among the most widely used are gentamicin and streptomycin. Aminoglycosides are cheap, and don't need refrigeration, which makes them useful in developing countries. The fact that they attack so many infectious diseases also makes them popular around the globe, particularly at a time when the declining potency of antibiotics is a major public health concern.

For years, scientists have tried to figure out how to inhibit the side effect of hearing loss while still maintaining

TONY RICCI (LEFT) AND ALAN CHENG HAVE BUILT A TEAM TO DEVELOP A SAFE REPLACEMENT FOR A TYPE OF ANTIBIOTIC THAT CAN CAUSE DEAFNESS. THE RESEARCHERS USE A PATCH CLAMP RIG IN RICCI'S LAB TO SEE WHICH FORMS OF THE DRUG CAN ENTER HAIR CELLS — CELLS CRUCIAL FOR HEARING.

the drugs' powerful antibacterial properties that save lives. Ricci's discovery, about a decade ago in that New Orleans lab, may provide an answer.

"If we can eventually prevent people from going deaf from taking these antibiotics, in my mind, we will be successful," Ricci says.

It was Ricci's grandmother who insisted that he get out of New York and be the first in his family to go to college. He worked in construction while he was in high school to help support his family and didn't consider college a useful option.

"The smartest thing I ever did was listen to my grandma," Ricci says.

C O N T I N U E S O N P A G E 3 7

Hear and now

BETTER,
LESS COSTLY
TREATMENTS
FOR HEARING LOSS
COMING SOON

As far as Amy Yotopoulos could tell,

her father, Edwin Lutz, was changing with age, the way most people do. He had become more introverted and quiet, less engaged. But he was still the same. He was simply finding everything harder to hear. As his six grandchildren were born and learned to talk, he had difficulty picking up what they were saying. Trying to keep up in any conversation wasn't just difficult, it was sometimes impossible. "If I didn't hear something right at the beginning, I just gave up. So I just kind of gave up on listening."

Lutz, who is now 76, was frustrated with his first pair of hearing aids, which he received about 12 years ago. He would only put them in if his wife, Peggy, suggested it, and then they would squeal or he'd still struggle to hear, only to give up and toss them back in the drawer. Yotopoulos watched as her father grew tired of saying "I can't hear you" to her and his grandkids. "And it was hard for the kids to take turns, speak clearly and slowly, face Grandpa, et cetera," she says. "So we all just figured this was the new normal."

For Yotopoulos, director of the Mind Division of the Stanford Center on Longevity, this new normal was unacceptable. How could a man whose daughter was an expert on healthy aging be unable to address

BY JULIE GREICIUS

ILLUSTRATION BY GÉRARD DUBOIS



his hearing loss? Yotopoulos was well aware how common it is for aging adults to be afflicted with hearing loss; how rarely they get adequate treatment; and how vast the impact of untreated hearing loss can be on their health, mobility, finances and relationships.

With access to the Stanford Medicine physician-scientists who are making advances in the diagnosis and treatment of hearing loss, Yotopoulos also knew that new solutions were within reach — not just for her dad, but for the millions of people who have hearing loss today or are projected to have it in the future.

According to the National Institutes of Health, “Approximately one in three people between the ages of 65 and 74 has hearing loss, and nearly half of those older than 75 have difficulty hearing.” A review of literature in the October 2017 *JAMA Otolaryngology* raised that estimate, stating that hearing impairment affects nearly two-thirds of Americans who are 70 and older. Simply put, adults older than 70 are more likely to have hearing loss than to have normal, healthy hearing.

Despite these statistics, fewer than 20 percent of people with hearing loss obtain treatment. The small percentage of people who address the issue, such as by getting hearing aids, don’t usually do so until eight to 10 years after their initial diagnosis — enough time for some of the conditions related to hearing loss to take hold.

UNDERSTANDING HEARING LOSS

THE WAY WE LIVE WITH HEARING LOSS, HOWEVER, IS IN THE MIDST of a revolution, with enormous changes ahead. New approaches to testing and more affordable and effective treatments are clearing the way for healthier hearing in aging adults. Those changes can’t come soon enough. Aging adults are less willing than ever to let hearing loss slow them down and are more open to wearing advanced, in-ear devices.

Yotopoulos says people might be more motivated to take action if they were fully aware of the health consequences of not being treated.

“We can’t say hearing loss causes these issues at this point, but it’s correlated with decreased mental health, such as depression, and increased risk of cognitive decline, dementia and death,” Yotopoulos says. “It’s correlated with your balance, risk of falls and sense of social engagement. And we now

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BECAUSE
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ANYMORE.’

know that social isolation has the same mortality and risk factors as smoking a pack of cigarettes a day, or as being obese.”

Because her dad had surmounted other serious health issues, his hearing loss seemed a relatively manageable problem. Still, it was a continual source of frustration. The simple joy of watching British television mysteries with his wife became a complicated activity full of missed moments and him asking questions. Lutz could no longer hear the sounds of the outdoors that he loved. And there was no joy in going to restaurants, where background noise made it impossible to follow conversations.

“I thought he was just kind of calmer or just wanted to watch things,” says Yotopoulos. “And it was a little sad because he wasn’t this ‘Hey let’s play a card game together’ kind of grandpa anymore.”

“Hearing loss is a potent isolator,” says Robert Jackler, MD, the Edward C. and Amy S. Sewall Professor in Otorhinolaryngology, professor of neurosurgery and of surgery at Stanford. “Human communication is nourishing not only to the soul, but also to the mind and, ultimately, the body. People who become isolated and unable to interact with others withdraw into an ever-closing circle that leads to unhappiness and depression for many.”

For older adults, that isolation has far-reaching consequences. “When you lose your hearing, you don’t just lose your ability to hear,” says Matthew Fitzgerald, PhD, assistant professor of otolaryngology-head and neck surgery at Stanford. “There’s evidence to suggest that the brain may reorganize, that the brain will change, when you have hearing loss and are deprived of sound.”

Losing our sense of sound as we age is, for most people, caused by the deterioration of cells deep in the inner ear known as hair cells. “It’s a popular misconception that hearing loss, when you grow older, is ‘nerve deafness.’ In fact, we know that the hearing part of the brain and the hearing nerve remain intact,” explains Jackler, who is chair of the Department of Otolaryngology-Head & Neck Surgery. Instead, most adults experience a gradual breakdown of “a relatively small population of hair cells that take vibrations in the air and turn them into nerve impulses the brain understands as sound.” Repeated exposure to loud noise — at work sites or concerts, for example — can expedite that breakdown.

As a boy growing up on a farm in South Dakota, Lutz

was a hunter. “We shot rifles and shotguns,” he says. “And we didn’t wear any hearing protection.” In 1965, when Lutz was 23, he began his service as a helicopter pilot for the Army, serving in the Vietnam War. “Even though we had flight helmets and earplugs, the high frequency of the turbines caused complete high-frequency hearing loss,” says Lutz. In 1987, his military retirement physical showed that Lutz still had hearing in the lower ranges, but over time he began to lose that as well.

“It wasn’t a single event that caused my hearing loss,” says Lutz. “It was a gradual progression, part of it age, and part of it the environment I was in.”

The onset of hearing loss as we age may be gradual, but the accumulated effect on our population is developing into an epidemic of drastic proportions. This is especially true in the United States as the baby boom generation — the 75 million babies born from 1946 to 1964 — has reached or is about to reach senior citizenship. The number of individuals of all ages with mild to complete hearing loss will balloon from just under 44 million today to nearly 55 million in 2030.

With such vast demand for audiological health care services, coupled with recent advances in technology and treatments, the hearing care industry is ripe for transformation. Even as the industry is changing, so are the aging individuals it serves. “It used to be that grandmother sat upstairs and knitted and came down for dinners and was with the grandchildren,” says Jackler. “Now seniors want to live active, full and socially engaged lives. They want to go to seminars, enjoy restaurants and be out with friends until a much later age.”

That’s certainly true for Ed and Peggy Lutz. While most of their friends near their home in the state of Washington travel south for the winter, the Lutzes go north. Ed Lutz is the youngest male member of his ski club at Big White in Kelowna, British Columbia. The oldest member is 90. “I’ve had two strokes and lost a third of my peripheral vision on the left side, so I follow my wife down the slopes now,” he says.

Lutz has also had two heart attacks, remedied by a pacemaker and defibrillator. Yet he and his wife still enjoy hiking and backpacking, sea kayaking, sailing on the lake, playing bridge, golfing, and volunteering at the local community civic center and the annual chamber music festival. “At our age, one can never stop because if you do, you will never get back.”

That desire to stay active and engaged as an aging adult can accentuate the stigma of hearing loss and of using hearing aids. For many adults, losing hearing is a signal of increasing

and inevitable physical fragility that can be profoundly difficult to accept. Wearing a hearing aid can feel like having that fragility openly on display. Many would rather live without it.

Couple this with the outrageous prices of hearing aids and the barriers to care feel insurmountable.

HIGH DEMAND FOR CUTTING COSTS OF CARE

HEARING AIDS COST ANYWHERE FROM \$1,000 TO \$6,000, which includes the device — or devices, as two are often needed — and the professional services to fit and program them. Few insurance companies provide coverage for hearing aids, though the full coverage the Veterans Health Administration provides is a welcome exception.

Hearing aids are the third most expensive tangible investment most families make, after a house and car. Yet the investment is still a good choice because the use of hearing aids has been shown to mitigate income loss up to \$22,000 annually for people with extreme hearing loss. Annual excess medical expenditures for U.S. adults with hearing loss who are 65 and older are estimated at \$3.1 billion, according to a study in the *Journal of the American Geriatrics Society* published in June 2014.

“It’s horrendous how expensive hearing aids are. They are enormously overpriced,” says Jackler. “The profit margin for hearing aids approximates that for popcorn at the movie theater.”

That movie-popcornlike profit margin may soon be a thing of the past, as the new wave of hearing health takes hold. On Aug. 18, 2017, the Over-the-Counter Hearing Aid Act, designed to provide greater public accessibility and affordability for over-the-counter hearing aids, was signed into law. The law will make it easier for people with mild to moderate hearing loss to access hearing aids. “The challenge,” explains Fitzgerald, “is getting people the right type of care they need for their level of hearing loss. Individuals who have more difficulty communicating will likely be best served by seeing an audiologist, while individuals who have less difficulty communicating should benefit from an over-the-counter device. What’s missing is a way to help triage or help guide patients as to what level of care they should be seeking.”

For family members like Yotopoulos and Peggy Lutz, having a way to help guide Ed Lutz to the right level of care would have simplified things. Recognizing that need — for people with hearing loss and their family members who

notice it — Yona Vaisbuch, MD, clinical instructor of otolaryngology at Stanford, is developing an online tool for front-line assessment “to help bring people over the age of 55 to try solutions like hearing aids.” First conceived in a six-month project with the Stanford Byers Center for Biodesign, the non-profit website WeHearYou will offer a short video on awareness, a basic hearing screening, an explanation of treatments and an option to input your location to find a provider.

“Today we know that age-related hearing loss doesn’t start when you’re 60 or 70. That’s when it becomes really symptomatic,” says Vaisbuch. “We now know that people in their 30s are already beginning to experience subtle decline.” His hope is that the website will be a way to screen and inform as many people as possible.

“When you have hearing loss, you spend a lot of time just trying to compensate for that,” says Vaisbuch. “We call it the cognitive load. You’re putting all your cognitive effort into hearing, instead of into the other things you’re doing. With time, those brain changes will not be reversible. That’s why we need to treat hearing loss as soon as possible.”

IMPROVING DIAGNOSTICS

BUT TO ADEQUATELY TREAT HEARING LOSS, PATIENTS MUST first have an accurate diagnosis — a key to revolutionized hearing care. Jackler and Fitzgerald are challenging the routine hearing tests of the past and are developing a new approach.

“The way hearing testing has been done for the past 60 years is threshold testing in a quiet room,” says Jackler. “Well, for most people, their problem is not how well they hear really soft whispers in a quiet room.”

“The reality is that when patients walk in the door, the No. 1 complaint they have is the difficulty of understanding speech in the presence of background noise,” says Fitzgerald, who is the chief of audiology at Stanford Health Care



EDWIN LUTZ AND his wife, Peggy, don’t let his hearing problems slow them down. They hike, kayak, backpack, sail, golf and enjoy time with friends and family. ‘At our age, one can never stop because if you do, you will never get back,’ he says.

and Lucile Packard Children’s Hospital Stanford. “At Stanford, we’re taking the lead in trying to make speech in noise the default test of speech perception in the audiology test battery. This small, but fundamental shift would be one of the most significant changes in how hearing testing is done in this country in decades.”

The change would be particularly beneficial for older people with hearing loss, Fitzgerald says, because “when you get older, the ability to extract speech from background noise gets a little worse than when you’re younger, and the existing test battery doesn’t account for that possibility at

all.” Testing a patient’s ability to communicate and understand speech may allow audiologists and physicians to parse the effects of aging from the effects of hearing loss.

While these new measures are part of the standard audiometric testing at Stanford, only some clinics nationally have incorporated them. “They are more often seen as something extra,” says Fitzgerald.

Changing decades of clinical practice doesn’t happen overnight, Fitzgerald says, and some audiologists question what it adds to their practice. His research aims to show how these measures can be readily integrated and to emphasize the additional information that can be gained from their use. The next, ideal step after that research is published, he says, would be for the governing bodies for both audiology and otolaryngology to recommend guidelines for speech in noise testing as part of the baseline audiological evaluation. “I’m optimistic that high-quality published research, in conjunction with maintaining a presence at national meetings, will facilitate this transition that is long overdue,” Fitzgerald says.

The more accurate the measure of a patient’s hearing difficulty, the more accurate and personalized treatment can be. Because hearing difficulty is highly individualized, from the degree and type of hearing loss right down to the shape of the ear, there’s no one-size-fits-all solution. With a broad selection of fittings, features and styles, a variety of hearing

aids can drastically improve hearing for people with mild to severe hearing loss right now.

“There’s been more development in hearing aids in the past seven years than in the past 70,” says Gerald Popelka, PhD, adjunct professor of neurosurgery, head of the Stanford Ear Institute Neuromodulation Research Lab and one of the inventors of the first digital hearing aid.

HIGH-TECH ADVANCEMENTS IN DEVICES

THOSE ADVANCES INCLUDE EVERYTHING FROM DIGITAL BLUETOOTH-connected hearing aids that work with devices like televisions and other sound systems to stream audio to designs that fit invisibly in the ear canal or with a low-profile shape around the ear. Each can be programmed to the individual frequency needs of the listener.

Even as today’s technology can readily solve the hearing difficulties of many people, the pace of innovation is still gaining momentum. Solutions to hearing loss are being developed both within the ear and beyond the ear. By the time that Generation Y — the only generation to outnumber baby boomers, and one that’s already accustomed to the regular use of in-ear devices — begins to reach age 60 in 2041, these innovations, along with others we cannot yet imagine, will be available.

“Increasingly,” says Jackler, “wearing something on your ear will be a badge of technological prowess rather than a marker of age and infirmity.” Jackler and his associates in Stanford’s audiology division and the Byers Center for Biodesign envision devices that are capable of doing much more than enhancing hearing for users of any age.

“It turns out that having a telemetry system attached to the human body has very important implications, not the least of which are for hearing,” says Jackler. “If you have something clipped on your ear that communicates out to a computer system, you have the ability to monitor oxygen, glucose, blood pressure and, through little EKG-like sensors on your chest, the electrical activity of your heart.”

All of this health monitoring could be available in the same device — Vaisbuch calls such devices “earables” — that stores and plays your music or audiobooks and connects to your phone or to audio text messaging. Such a device could, for example, alert you if you’re starting to cross the street when

a car is coming or discreetly remind you of the name of the host’s spouse when you arrive at a party. As voice-to-text technology improves, it could eliminate the need for a keyboard, reducing carpal tunnel syndrome. It could be programmed to lower background noise and amplify voices in spaces that are often especially challenging for people with hearing loss, such as restaurants or theaters. It could also use noise-cancelling technology to silence the environment when desired.

“The ear becomes an important part of this enriched linkage between the human body and machines,” says Jackler. “You’re looking at a coupling of man and electronic device that really changes our understanding of how diseases function.”

Another intervention that Jackler hopes will become a reality in the near future is a biological cure for hearing loss. Through the Stanford Initiative to Cure Hearing Loss, more than a hundred scientists and technicians are working to cure inner-ear hearing loss — the type that results from hair cell degeneration — which remains incurable today.

Stefan Heller, PhD, the Edward C. and Amy H. Sewall Professor and professor and vice chair of research in otolaryngology, was the first to discover the stem cells within the inner ear of mammals that can be converted to hair cells. “We know that hair cells regenerate in birds, reptiles and amphibians,” says Jackler, “but not particularly in mammals such as humans.”

Under Heller’s leadership, the hearing loss initiative is exploring the manipulation of pluripotent stem cells — foundational stem cells that exist in the patient’s own body, in this case in the ear itself — to restore hair cells and allow patients to hear again. So far, the team has seen success only in mice.

“We’re very hopeful that this will come to humans in the next decades and that what was heretofore incurable will become curable,” says Jackler, “and that we’ll be able to rejuvenate hearing in the elderly, in the child born deaf and in someone who’s lost hearing from a variety of medical conditions.”

Until that cure is available, Jackler is still enthusiastic about the increasing options available to patients. “I have a huge optimism about the future of our ability to help people with hearing loss,” he says.

For two days in March 2017, the Stanford Center on Longevity gathered international experts in a broad range of fields including audiology, psychology, engineering, architecture and health advocacy to focus on improving

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MARKER
OF AGE AND
INFIRMITY.’

CONTINUES ON PAGE 39

MUSIC AND THE MIND

She is known as “the people’s diva,”
and when you meet famed
lyric soprano Renée Fleming
you immediately know why.
She’s open, engaging and friendly.
Perhaps it’s her upbringing in
Rochester, New York, as the daughter of
two public school music teachers.

It’s easy to see Fleming as approachable and one of us. Yet, Fleming has flown through the stratosphere in the arts. She’s performed at the Nobel Peace Prize ceremony, the Beijing Olympics, the Brandenburg Gate to celebrate the 25th anniversary of the fall of the Berlin Wall, Buckingham Palace for the Queen’s Diamond Jubilee, the Lincoln Memorial for the inaugural celebration of President Barack Obama and every major concert hall in the world. In 2013, Obama awarded her the National Medal of Arts, America’s highest honor for an individual artist. In April, she added one more achievement, making her Broadway musical debut in a new production of Rodgers and Hammerstein’s *Carousel*.

A project close to her heart and head is a collaboration she’s spearheading between the John F. Kennedy Center for the Performing Arts, where she serves as artistic advisor at large, and the National Institutes of Health, in association with the National Endowment for the Arts. The initiative, Sound Health: Music and the Mind, explores how listening to, performing or creating music involves brain circuitry that can be harnessed to improve health and well-being.

Recently while Fleming was on campus for a Stanford Live performance and a presentation on neuroscience and music, she sat down with Paul Costello, executive editor of *Stanford Medicine*, to talk about the left-brain/right-brain initiative, which she launched with NIH Director Francis Collins, MD, PhD.

COSTELLO: It almost sounds like the setup to a joke: Three Supreme Court justices, a renowned scientist and a world-famous opera singer walk into a Washington dinner party.

FLEMING: Well, it really was an extraordinary event. I had never met Francis Collins. I had met Justices Scalia, Ginsberg and Kennedy at a concert series at the Supreme Court. Dr. Collins brought his guitar and we kind of interrupted the band and took over with an impromptu sing-along with everyone. I had just been appointed artistic advisor at the Kennedy Center. At one point during the evening I turned to Dr. Collins and said, “What do you think about all of this research about the brain and music? Might we collaborate and bring these two great institutions — the Kennedy Center and the NIH — together?” My idea was to amplify the research to the larger public. I didn’t feel people really knew how powerful it was. He completely embraced it.

COSTELLO: Was there a particular aspect of the research that intrigued you?

FLEMING: One of the things I learned over the years was that, for some inexplicable reason, many doctors are amateur musicians. I’ve always wondered: What’s the connection between medicine and music? I started to read and learn and found there were extraordinary connections with basic science, therapies or treatments, and child development. Those were the areas I thought were really interesting.

COSTELLO: Do you have specific goals for the collaboration?

FLEMING: The first goal is to move music therapy forward as a discipline, make it more widely understood and more widely supported. The second is to educate the public and enlighten people about the

SOUND WAVES

The art and science of hearing

power of music to heal. Take Alzheimer's. Why can somebody who doesn't recognize anyone around them sit down at a piano and play beautifully or remember the words to songs and sing along? There is an emotional power, an underpinning of who we are as human beings, that exists in this realm of music.

COSTELLO: Does your voice heal you?

FLEMING: That's an interesting question. I think singing, definitely, and music in general have a huge power over me. When I sing the *Four Last Songs* of Richard Strauss, which I've sung more than anything in my repertoire, in the last piece, I am in a meditative state. My breathing slows down. I can suddenly lift out of my daily life, and that happens every time. So, I would say, yes.

COSTELLO: Have you ever analyzed the process of what you're going through while you sing?

FLEMING: I went to the NIH and participated in an fMRI imaging study that actually looked at my brain when I was performing. It's an incredibly fascinating scan and it's remarkable how much the brain is activated by music. It has a broader impact on the brain than almost any other activity. This is what scientists are beginning to understand.

COSTELLO: You were in the fMRI machine singing?

FLEMING: I was in the machine for two hours. I didn't quite understand what I was signing up for. (laughs) I sang a snippet from a folk song, *The Water is Wide*, for about 60 repetitions. I had to sing it over and over again, lying down, without being able to move. I sang the words, spoke them and imagined the words.

It was all quite interesting. The most powerful impact on my brain was imagining singing. It was more far-reaching than either singing or speaking. The researchers said, in my case, because I sing all the time, it's second nature. I could relax a little in the singing part. But in the imagining part, I had to really focus. The MRI is very loud!

COSTELLO: You chose a Scottish folk song. Why that particular song?

FLEMING: I've always found power in folk music. One of the ques-

tions I have is: Why are certain songs universal and universally loved?

COSTELLO: What are the universal songs for you?

FLEMING: In my own performances, it's definitely Puccini's *O mio babbino caro*. No matter where I sing in the world, people respond to that. Others are *Amazing Grace*, Leonard Cohen's *Hallelujah*, and *Ave Maria*.

COSTELLO: Were there moments in your career when you were especially intrigued by the connection of brain to music?

FLEMING: There are two things that have plagued me throughout my career. One was stage fright. The other was somatic pain, caused by performance pressure. In order to understand these two things, which in my 30 years of singing have not been widely supported or understood by medicine, I had to do a great deal of reading and try to figure it out myself. I've been extremely interested in the mind-body connection.

COSTELLO: What do you tell young opera singers about how to deal with stage fright and self-doubt?

FLEMING: I break it down. One is to understand the root of it. The other is to really change the way you think about it, in terms of your cognitive approach. People don't come to a performance to be judgmental, by and large. They don't come with a scorecard. They come to relax and enjoy themselves. Beverly Sills wrote a book about public speaking. When she approached an audience, she talked about having a benevolent sense of sharing. I immediately understood: Turn the way I approach my experience on stage away from thinking the audience is looking at me to thinking that I am sharing with them. That really clicked.

COSTELLO: What do you hope comes out of the brain and music initiative?

FLEMING: That we, as a society, appreciate the arts more, value the arts more and understand that when the arts come into a community and rejuvenate it, that's important. We still kind of think of the arts as soft and light. Yet, the science is there. It's been proven that kids benefit tremendously from studying a musical



ALL EARS

A
SAMPLER
OF
INTELLIGENT
LISTENING
TECHNOLOGIES
EMERGING
FROM
STANFORD

BY KRIS NEWBY

ILLUSTRATION BY DAVID PLUNKERT

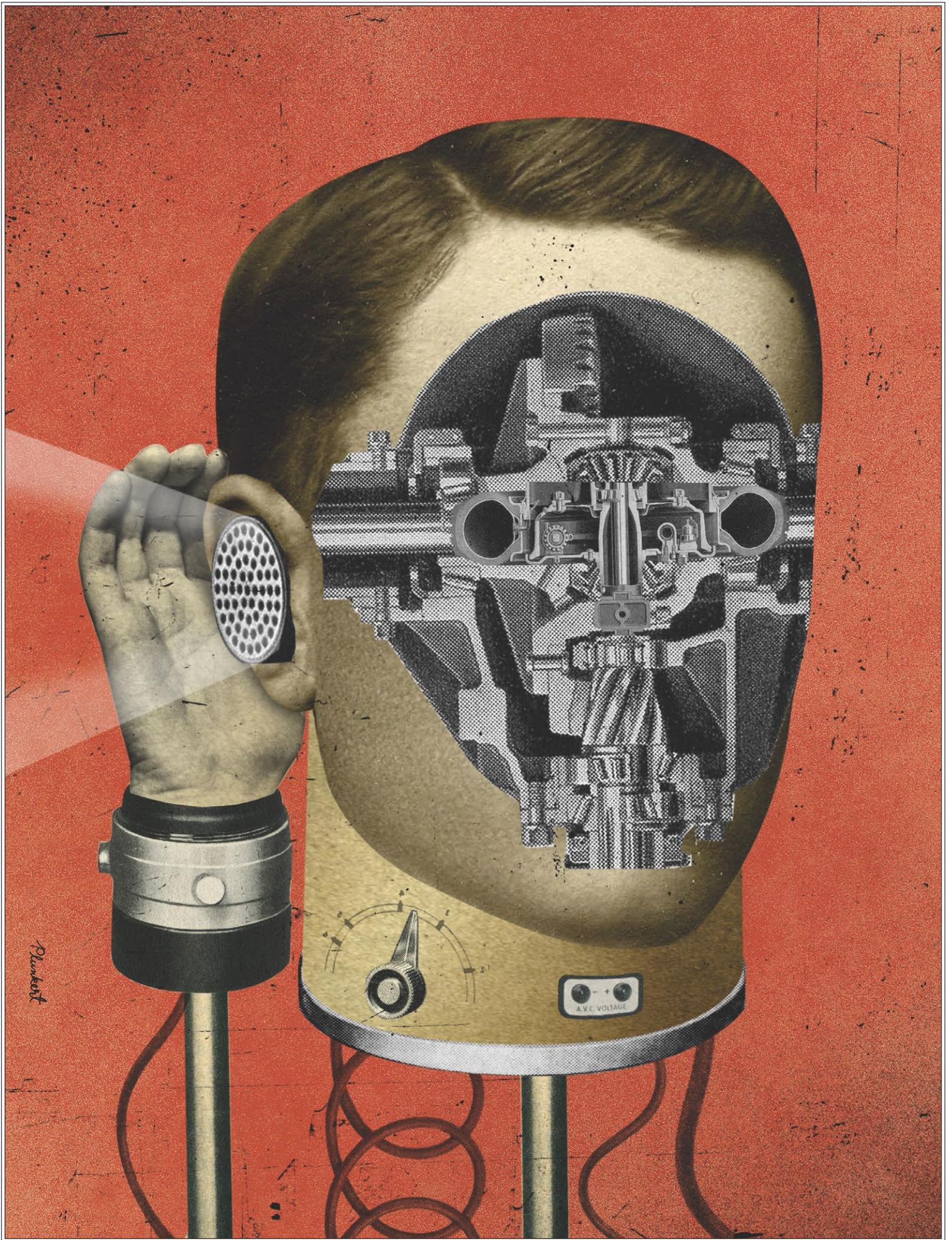
Machines are excellent listeners.

As you speak or type, circuits inside your smartphone, smartwatch and virtual assistant are collecting information about you, then converting it into digital patterns. These patterns are wirelessly sent to rooms full of whirring, blinking supercomputers that translate them into words, meanings and actions. Behind this technology are decades of artificial intelligence research and millions of lines of computer code. We stand on the shoulders of giants when we say, *Play Beethoven's Fifth*, and our device responds with music to our ears: “da-da-da DUM,” the opening of the composer’s most famous symphony. Today, Stanford Medicine researchers are exploring ways to use intelligent listening technologies, natural language processing, machine learning and data mining to deliver better, more efficient health care. Here are a few of these projects.

MENTAL-HEALTH CHATBOTS

Until the middle of 2013, if someone said “Siri, I feel like jumping off a bridge,” the conversational agent inside an iPhone would reply with a list of nearby bridges. When this made the news, it was a wake-up call

CONTINUES ON PAGE 39



Plumbert

A.C. VOLTAGE

TO HEAR AGAIN

BIRDS REGROW

Hunkered over her computer,

Amanda Janesick, PhD, a postdoctoral scholar studying the biology of hearing, points to a series of microscopic images on the screen. The time-lapsed cross sections of a chicken's inner ear show multitudes of hearing cells dying off and multitudes of new ones replacing them.

This is interesting to Janesick — and many others concerned about hearing loss — because these cells function similarly in humans, with an important difference. In birds and mammals, thousands of these hearing cells, called hair cells because of their hairlike cilia, are hidden deep inside the fluid-filled cochlea, a tiny, bony structure. For a human or a chicken to hear, the swaying cilia on the hair cells sense sound vibrations from the outside world. The vibrations cause them to deflect, which opens pores or channels that allow electrical signals to be sent via the auditory nerve to the brain, which interprets the signals as sound.

Here's the key difference: If these hair cells are destroyed in humans, they lie around like flattened wheat after a rainstorm, permanently powerless to help us hear. The cells die for various reasons, including injuries, aging and loud noises. And no new cells replace them.

But in birds, amphibians and reptiles these cells grow back. So birds, unlike humans, never go permanently deaf. Scientists want to make humans more like birds.

"The goal is to follow the trail of these regenerating cells in birds," says Stefan Heller, PhD, professor of otolaryngology-head and neck surgery, who heads the lab where Janesick is working. "Then we have to figure out why this trail is not working in mammals. What are the missing parts? Maybe we will discover one critical trigger and we can cleverly fix this trigger in mammals."

New research in Heller's lab could finally lead to cures for hearing loss in humans by helping scientists understand the stepwise process by which individual cells, rather than entire groups of cells, regenerate into functioning hair cells.

"A fundamental piece is still missing," says Heller, who for the past six years has been using new tools to figure out how thousands of unspecialized cells, such as stem cells or progenitor cells, transform into hair cells. "We don't know how regeneration is being orchestrated. When a hair cell is dying, what signal is this hair cell

sending out to a neighboring cell, and what activates these neighbors to start the regenerative process?”

This search for biological discoveries in hearing loss has drawn the attention of biotech companies attempting to develop new products based on research from scientists like Heller. (Heller is a scientific adviser for one of those companies, Inception 3 Inc.)

WITNESSING NEW CELLS ARISE

In the chicken cochlea images in Heller’s lab, Janesick points to groups of supporting cells that are visible beneath the rows of hair cells — the progenitor cells. It appears that, as time passes, these cells turn into, or create, new hair cells.

Though the chicken cochlea is roughly banana-shaped and the human version looks like a snail shell, both are similarly filled with thousands of hair cells — 10,000 in chickens, 15,000 in humans. To witness how hair cells regenerate, Janesick first injected an antibiotic known to be toxic to hair cells directly into a chicken’s cochlea. Her images show the progression as the drug kills off

ty much nothing about how it works. It just seemed that this is an area of biology that still had open questions, lots of challenges. When people started asking me, ‘Why in the world would you choose a topic like that?’ — I realized that I had found my place.”

By 2002, Heller had gained international attention for being the first to identify stem cells — undifferentiated cells that can develop into various specialized cells — that reside within the inner ear. Over the next six years, his lab successfully developed mouse cells from these stem cells that looked and acted just like the animal’s inner-ear hair cells. In 2010, they published a study in *Cell* reporting these results as a major advancement.

The researchers hoped to perfect the recipe in human ear hair cells so they could generate the millions of cells that would be needed for transplantation into the ear. But they couldn’t get the cells to do their bidding.

“The early human ear cells we generated were just not stable enough. No one could figure out how to keep the cells on the desired inner ear trajectory; they always became some-

DAMAGED INNER EAR CELLS. WHY CAN’T WE?

BY TRACIE WHITE

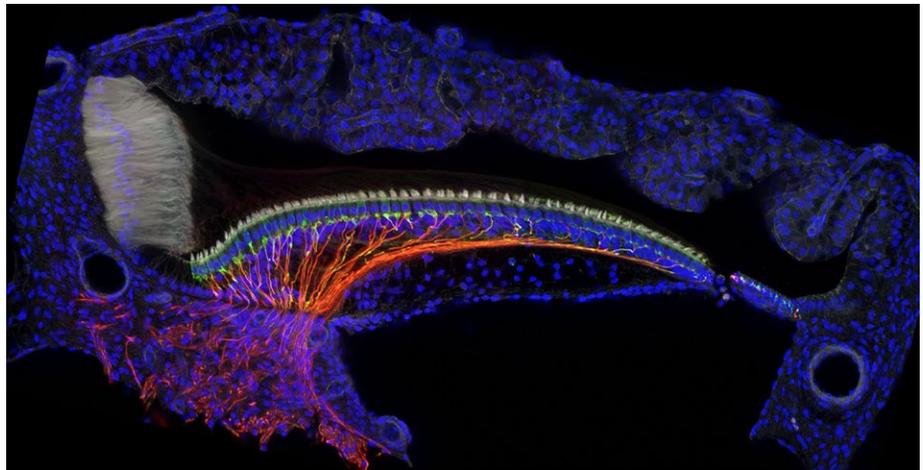
the hair cells within 24 hours, and then how multitudes of supporting cells grow rows of healthy, new, cilia-sprouting hair cells during the subsequent two weeks.

“We need to learn a lot more about those supporting cells,” says Janesick, a developmental biologist whose mild hearing loss helped spur her interest in working in Heller’s lab. “What are they, what do they do, how do they communicate with each other? And, ultimately, why can these cells regenerate hair cells when similar supporting cells in mammals appear to be nothing but a dead end?”

THE GENESIS OF HEARING LOSS RESEARCH

Heller’s interest in hair cells goes back to 1994, when he had just received a PhD from the Johannes Gutenberg University in Mainz, Germany, and was seeking an interesting project.

“I was literally looking through the book *Principles of Neuroscience*, and I found a chapter on hearing and hair cells,” Heller says. “The ear appeared so complex, and I knew pret-



A TRANSVERSE SECTION THROUGH THE MIDDLE OF AN EMBRYONIC (DAY 20) CHICKEN COCHLEA SHOWS NEURONAL CONNECTIONS TO HAIR CELLS. THE NEURONAL CONNECTIONS ARE COLORED GREEN AND RED. HAIR CELL BUNDLES ARE WHITE.

thing else. That was the end of the line for us,” Heller says.

That’s when his lab turned to technology to help understand how individual progenitor cells develop into hair cells in birds.

“We figured out that we had to get to the point where we understand what the thousands of individual cells are

C O N T I N U E S O N P A G E 4 0

plus

EXPLORING THE REALMS OF MEDICINE AND HEALING



Are you my doctor?

TOWARD A WORLD WHERE
A PHYSICIAN IN A WHEELCHAIR
IS NO BIG DEAL

By Cheri Blauwet, MD

ILLUSTRATION BY RIKI BLANCO

SEVERAL YEARS AGO, WHILE IN MY SECOND YEAR of medical residency, I was in my wheelchair in line at our hospital cafeteria. A man who came behind me gave me a warm look. After a few moments, he looked down and politely asked, “You look like you are doing pretty well. When are you going to be discharged?” I paused as my internal debate swirled. How to reply? Anger? Disdain? I settled on a measured approach and said, “Actually, I work here.”

These kinds of encounters occur frequently for those of us in medicine who don’t fit society’s profile of a prototypical doctor. In this instance, rather than noticing that I was an early 30-something, confident female with a stethoscope around my neck and a badge reading “Dr. Blauwet,” my wheelchair was the only thing this man saw. Moreover, he equated my wheelchair with illness and vulnerability, rather than empowerment.

Moments like this beg the question — what do people expect doctors to look like? Although we have come far since the days when medicine was dominated by tall, Caucasian men with white hair, it is clear that physicians are still profiled. Almost all physicians who are female or from marginalized racial and ethnic backgrounds relate stories of patients mistaking them for a nurse, janitor or

other uniformed staff. Recently, the story of Tamika Cross, MD, brought this issue to light after going viral on social media. During a flight from Detroit to Houston, passengers were asked, “Is there a doctor on board?” Although Cross, a black, female gynecologist, offered to assist the injured passenger, flight attendants questioned her credentials and qualifications and rejected her help, seemingly based only on her appearance.

While it’s less discussed, people with disabilities who are trying to build a career in medicine are similarly dismissed. Although people with self-reported disabilities account for 15 percent to 20 percent of the adult population in the United States, a survey of medical school deans (reported in May 2012 in *Academic Medicine*) demonstrated that students with physical or sensory disabilities represented less than 0.5 percent of graduating medical students. That proportion becomes higher, reaching 2.7 percent, when students with attention deficit hyperactivity disorder, learning disability or psychological disability are also included in these figures, according to a survey reported Dec. 6, 2016, in *JAMA*.

It is also important to note that disability is often under-reported for fear that it will be perceived as a sign of personal weakness — a finding published July 2015 in *Academic Medicine*. We would find this degree of disparity unacceptable when considering other personal attributes. Imagine if the representation of women in medical school deviated far from 50 percent. Women physicians would be rattling the cages and demanding change. Unfortunately, for a variety of reasons, the response from the disability community has been more muted.

I believe that a diverse physician workforce helps reduce bias among

physicians and improves patient care. Many patients seek to have a physician with a cultural lens that is similar to their own. It is important, then, to note that almost all patients will encounter disability at some point in life. In fact, those of us within the disability community often joke that everyone else is “temporarily able-bodied.”

DISABILITY IS UNIQUE in that it can be transient or permanent, and the incidence of disability is directly correlated with aging and the presence of chronic disease. For those rare souls not personally touched by disability, it is almost assured that a close family member or friend will be impacted. Does it not make sense, then, to assume that physicians who have a personal experience with disability would bring to the table a heightened level of empathy toward patients, and thus be a healthy and positive addition to our workforce?

I remember my experience in medical school and the poignant moments when I realized I was transitioning from patient to physician. One of my primary motivations for choosing a career in medicine had been my early experiences with the health care system. I injured my spinal cord at a very young age and, even then, had a canny sense of which doctors were truly empathetic versus simply going through the motions.

As a medical student, I couldn’t escape the irony of being back in a hospital, a very familiar environment, but with a completely different lens. That long wait time for an outpatient clinic visit, frustrating to patient Cheri, was suddenly very understandable to medical student Cheri. When sitting in class learning about the basic tenets of neurology, I understood the physi-

ologic causes of some of the symptoms I had experienced as a result of my spinal cord injury. Although it is true that knowledge is power, it can also be disquieting: Learning statistics such as rates of depression and the shortened life expectancy in people with spinal cord injuries gave me pause.

So, where do we go from here? Several initiatives are underway to both increase the presence of people with disabilities within the medical profession, and also to enlighten all medical trainees about the importance of understanding the social context of disability to provide better patient care. A new report from the Association of American Medical Colleges, *Accessibility, Inclusion and Action in Medical Education*, provides an updated framework for optimizing the potential for learners with disability in a health care environment.

Ultimately, we are striving to normalize the presence of people with disabilities in medicine and debunk what is traditionally called the medical model of disability in which disability is seen merely as a diagnosis, a pathology or an individual flaw. This must

be replaced with the biopsychosocial model of disability in which disability is understood to be a complex interaction between the individual and his or her environment, inclusive of personal factors (for example, resilience and motivation) and external factors (for instance, accessible ramps and bathrooms).

Increasing the representation of people with disabilities in medicine is one important piece of the solution. Building on the success of prior social media campaigns such as #ILookLikeASurgeon, the hashtag #DocsWithDisabilities was developed as part of an advocacy campaign from the University of

One of my primary motivations for choosing a career in medicine had been my early experiences with the health care system.

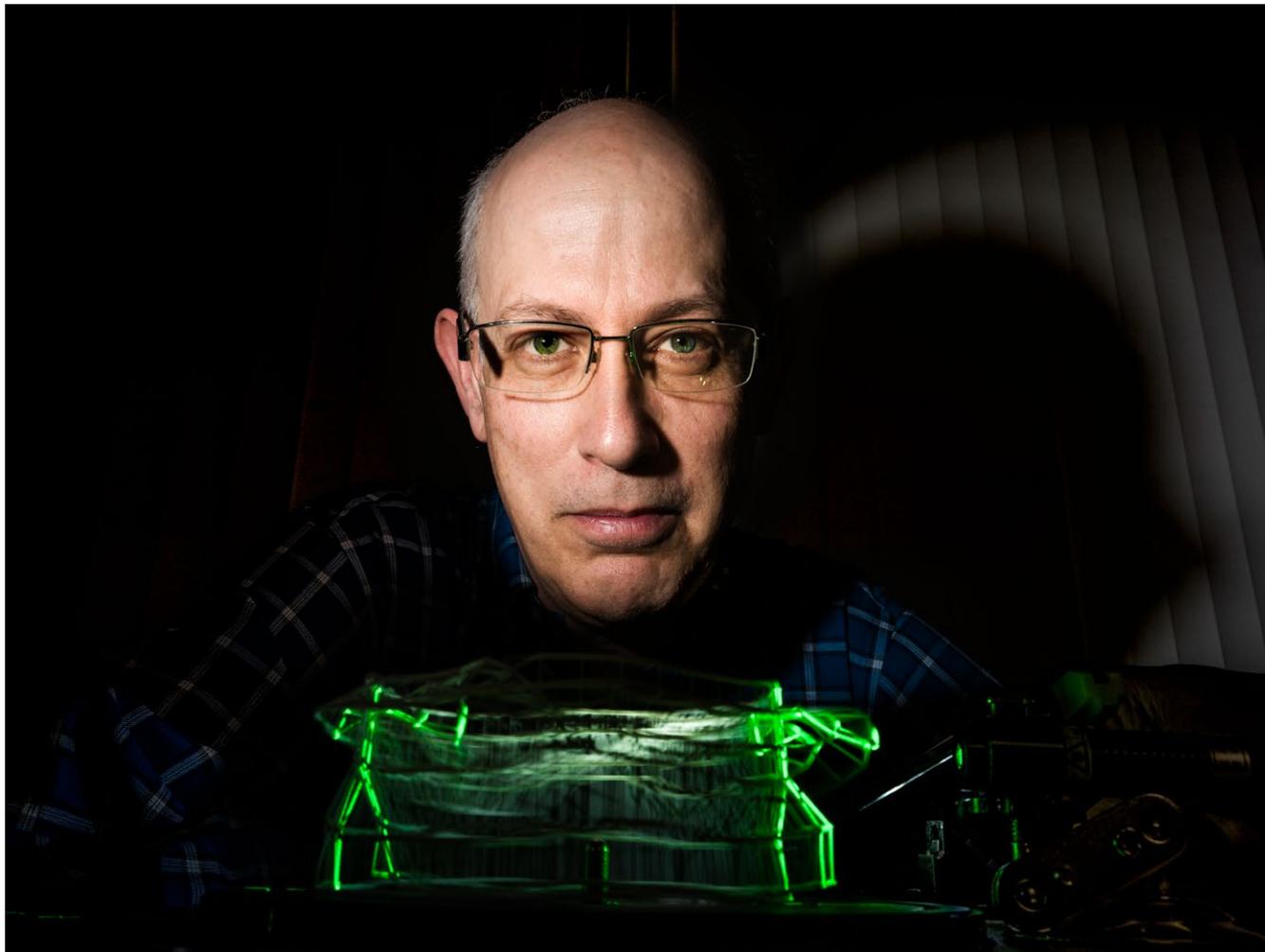
CONTINUES ON PAGE 41

Say it with sculpture

BUILDING KINETIC CONTRAPTIONS TO BRING DATA TO LIFE

By Bruce Goldman

PHOTOGRAPHY BY MAX AGUILERA-HELLWEG



DAVID SCHNEIDER BUILDS MOBILE MACHINES TO CONVEY COMPLEX DATA.

ON A WALL-MOUNTED SHELF IN the office of David Schneider sit two dozen or more empty Diet Coke bottles of varying shapes and sizes. They're emblazoned with various languages, testifying to all the places he's downed one of the beverages. He's not a coffee drinker.

There's also a nice bug collection displayed on the wall. Schneider, PhD, professor of microbiology and immunology, has been collecting bugs since his childhood in Ottawa, Ontario.

"I've always loved biology," he says. When he was in 12th grade, he won first place in an international science contest, besting the future founder of Amazon, Jeff Bezos.

And you can't help but notice, atop a packed bookcase, an assortment of odd

little wooden contraptions. They're kinetic sculptures that Schneider built to represent data that would otherwise be hard to comprehend.

"David's office is a unique environment that really reflects how unique he is," says Denise Monack, PhD, professor of microbiology and immunology, whose lab is adjacent to his. "He's extraordinarily creative."

If Schneider's office seems a bit busy, it's in part a reflection of his pace. As chair of the Department of Microbiology and Immunology, he oversees a complex of 150 people. He also teaches and does a lot of research.

Schneider's research generates lots of data, which is where the contraptions come in: Sometimes it makes more sense for him to plot that data in more than two dimensions. He calls his creations data sculptures.

CIRCULAR REASONING

SCHNEIDER FOCUSES on infectious diseases and their effects on infected hosts. Getting sick and recovering are two different sides of a circular journey, he says.

"The path you take back to health isn't the path you take to getting sick," he says. "It's a loop." The precise scientific

swing and hit the ball to left field, you bunt or the umpire calls, "Ball four!" In any case, you're on your way to first base. At this stage, the pathogen load is increasing, and your immune system is kicking in and making you feel worse. By the time you reach second, you're at your maximum point of sickness.

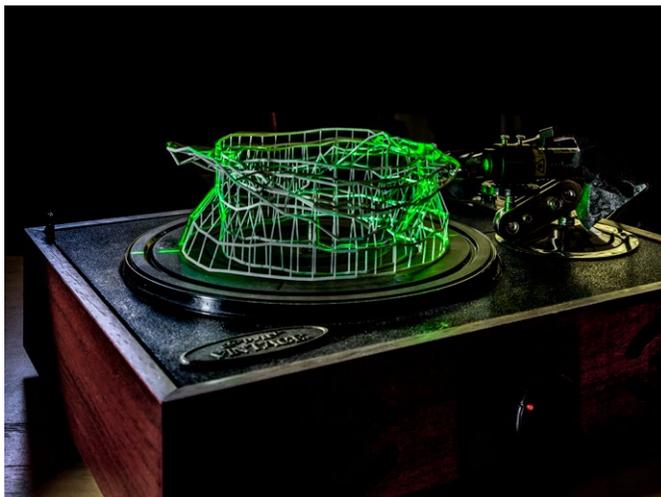
Recovery is analogous to scoring a run, having rounded all those bases. However, you can't score, or return to full-blown health, by going in reverse from second base back to first and then home. Very different things are happening in your body when you're approaching or standing on third base as opposed to first base. Though, from the stands, those two bases may appear juxtaposed, it would be a mistake to think first base and third base are equivalent. The internal states of the players standing on those bases are quite different. You might want

UPS AND DOWNS

MALARIA INFECTS more than 200 million people a year, making them really ill. About 400,000 of those people, mostly children, die every year, Schneider says. "We don't have a vaccine. There's resistance to almost all the drugs we have. We need new ways of fighting the disease."

Schneider's group has been doing experiments with malaria-infected mice, monitoring many aspects of their physiology. "And we notice, in these mice, that the levels of various cell types and immune-signaling chemicals in the blood go up and down as the animal gets sick, then recovers or dies." A given drug may work only during a limited portion of this cycle.

What he's learned from his studies is that to treat a patient most efficiently, it would be great to know when the pa-



term for this kind of loop is hysteresis.

Not that the loop necessarily has to be represented as a circle. It could be depicted, for example, as a baseball diamond. When you're first infected, you're standing at home plate — analogous to your initial state of good health. Then the pitch comes — that is, you are infected by who knows what — and you, the infected host, respond in one of various ways, depending on the pathogen and on your initial condition: You

to give the third-base patient an entirely different set of medications from those suitable for a first-base patient. Maybe you should give one antimicrobials and rehydrate the other.

Take malaria. When infected humans or mice are at their sickest, they're already well on their way to eliminating the microbes that cause the disease.

tient got infected. But that's somewhere between tough and impossible.

"We can't expect a child suffering from malaria to tell us when they were bitten by an infected mosquito," Schneider wrote in his study of malaria-infected mice and human patients published in *PLOS Biology*.

That study showed that infecting

FOR HIS FIRST DATA SCULPTURE, DAVID SCHNEIDER TRACKED HIS WIFE'S MOVEMENTS WHILE SHE DANCED AND MAPPED THEM ONTO A PLASTIC FRAME. A GREEN LIGHT THAT SHINES ON THE THE SCULPTURE AS IT SPINS ATOP A RECORD TURNTABLE REPRODUCES HIS WIFE'S MOTIONS.

mice with a malaria parasite resulted in a predictable set of changes in the blood levels of nine different cell types and immune-signaling substances as the mice first got sick and then recovered or, if they got too sick, were euthanized. By looking at the ratios and absolute levels of certain measured cell types and chemicals, the researchers could identify just where a mouse was along the looping path from health to sickness to recovery or death, and how likely it was to die barring further intervention.

In the same study, Schneider and his colleagues extended the findings to humans by looking at blood from children who had or hadn't been infected with malaria. Human infection, they showed, also follows a looping path, and the order of cellular and molecular ups and downs along that path rise and fall in the same sequence as in mice. That sequence provides a clue as to where a patient is in the sickness cycle, and factoring in the level of one or more blood markers in a patient might give you a good sense of how much danger he or she is in.

Nine is a big number. "If you're measuring nine things in a sick animal, it's hard to graph, not to mention grasp, nine different variables at one time," Schneider says. "You can lose some information. You want to emphasize that as one thing goes up, another comes down."

Having encountered difficulty in communicating such multivariate, circular data findings, Schneider increasingly turns to building data sculptures. One looks like a wooden rotisserie holding wooden pieces of "toast." The "rotisserie" is actually an open-front box. Its "skewer" is a long wooden axis running horizontally from one side of the box to the other side. The axis can be turned via an externally positioned crank.

The thin pieces of "toast" skewered inside the box are in fact slim disks, each irregularly shaped in its own particular way, that act as cams.

Each cam approximates a circle whose radius keeps

changing at different points along the rim. The radius of a cam at any given point represents the level, at a particular point in the sickness/recovery cycle, of one of the nine cell types or substances Schneider's team measured in malaria-infected mouse blood.

Astride each of the nine cams sits the figure of a man's torso. The men form a line along the box's top. When you turn the crank, they variously rise up, raising their arms to the heavens, or they sink down, arms back at their sides, as each is displaced idiosyncratically by its underlying, oddly shaped cam.

TURNING THE CRANK

THE LEFT-MOST LITTLE man goes up, then the next, then the next, etc. Schneider turns the crank some more and the first little man starts to come back down even as the ones to the right of it are still rising. The rise and fall of the serially adjacent little men occur in a left-to-right ripple as the crank turns.

"It looks like a wave," Schneider says. "You might have missed that if you were looking at numbers or a graph, or just focusing on one point in time. But when you look at it this way, you can't help but see that there's a wave moving through the data over time."

By analyzing the ratios and phases and rates of the rise and fall of all of the parts of this data sculpture, Schneider has shown it may be possible to figure out where in the disease-recovery cycle a patient is.

The hope is to eventually be able to predict early on whether a patient is headed for recovery and, if not, how to best treat the patient based on where he or she is in the disease cycle.

"I think these sculptures show the cyclical nature of infections better than any graph I've been able to use previously," Schneider says. "But I still have to figure out how to publish these things. The journals always want flat pictures. We have to find a way to get around that."

Grant writing, too. "The proposal formats often only let you submit a flat PDF.

I've snuck movies into my PDFs in the past. But the granting agencies immediately banned doing that."

From 2013 through 2016, Schneider, who teaches year-round, began offering postdoctoral scholars and graduate students a 10-hour course in scientific animation. In spring 2017, Schneider switched to teaching similar classes, between quarters, in data sculpture. These classes, which are limited to a dozen students, typically attract as many as 50 applicants.

Katharine Ng, PhD, a postdoctoral scholar in bioengineering, has been Schneider's teaching assistant for both the scientific-animation and data-sculpture courses. "David's always open to new visualization techniques," she says. "He's always looking for ways to, first, convey science to lay audiences, and, second, force his fellow scientists to confront his data in a new way, hoping that maybe they'll catch some new aspect or perspective they might have otherwise overlooked." **SM**

— Contact Bruce Goldman at goldmanb@stanford.edu

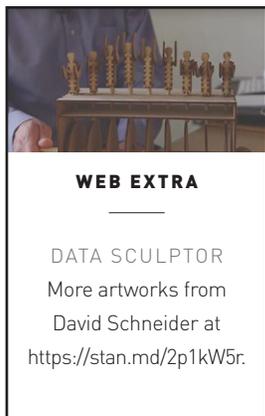
FEATURE

Are you listening?

CONTINUED FROM PAGE 13 and director of Stanford's Clinical Excellence Research Center, to develop new models of care that build on that kind of trust.

Glaseroff and his wife, Ann Lindsay, MD, left Humboldt County in 2011 to create the Stanford Coordinated Care program, basing it on their long-time family practice in Arcata, California, and on ideas gleaned from their more than 15 years of working with the Institute of Healthcare Improvement and other pioneers in the national movement to redesign primary care.

The coordinated care program is designed to cut costs for Stanford's self-funded insurance plan by treating the 5 percent of employees and their dependents whose care represents 50 percent of the plan's cost. The approach is meant to keep chronically ill patients from hav-



ing repeated setbacks and hospital visits by making them partners in their own wellness. Every team member knows the patients well and focuses on goals the patients identify.

The core principle is to engage people, to just sit and talk with them, and show them respect, Glaseroff says. “And the way to engage with them is listening, and it’s focusing on what they care about, even if it seemed trivial compared with what we care about,” he says. “But I don’t think it is trivial. It turns out to be of critical importance.”

Glaseroff believes the practice can apply in all areas of medicine where there’s continuity. “It isn’t just come in, get something done and never see you again,” he says.

“What we figured out is that, if everybody was trained in this approach and we were really consistent with it, we got incredible efforts out of the patients.”

Zulman says she’s intrigued by the potential to address the challenges that get in the way of such successes by taking something that seems “vast and fairly abstract” and designing and implementing concrete interventions that make a difference for clinicians.

That could result in rituals that foster human connection during patient history-taking and exams or could lead to new care models where physicians spend less time interacting with electronic health records and have more autonomy to determine how much time they spend with individual patients.

“It’s actually a really challenging problem,” Zulman says. “If there were a simple solution, and all you have to do is make eye contact and we’re done, we would have figured that out already.” **SM**

— Contact Patricia Hannon at phannon@stanford.edu

FEATURE

Sound research

CONTINUED FROM PAGE 17
nonresponsive, or they might fall asleep suddenly. In the public eye, this type of seizure more often flies under the radar, but that’s not to say they’re less threat-

ening to health. Parvizi says there’s now a stockpile of evidence showing that prolonged silent seizures are damaging to the brain, especially in children, whose brains are still developing.

“Right now, patients need a trained neurologist to detect a seizure. It may be controversial, but my goal is to enable anyone to detect them — all kinds of physicians, nurses, medical trainees.”

Even parents.

“You want moms and dads to be able to know if their kid is having a seizure so that they seek out professional attention,” Parvizi says.

In May 2017, the FDA gave the green light to Parvizi’s invention, and he has since tested the stethoscope’s capabilities in several hospitals, finding encouraging results.

“This could change health care dramatically when it comes to monitoring brains.”

POWERING IMPLANTABLE MEDICINE

PLACE TWO GRAINS of rice next to each other and you’ve about replicated the size of a rather savvy, next-generation medical chip devised by Amin Arbabian, PhD, assistant professor of electrical engineering. The chip is an implantable device, like a pacemaker or nerve stimulator, but is set apart by the way it’s powered — not by batteries or wires, but by sound.

“It has been a long-standing challenge to make medical devices as small as possible and operate deep in the body,” says Arbabian. “Ultrasound enables that.”

Ultrasound’s long-term use in fetal imaging has earned it a reputation in medicine for being safe and dependable, making it a prime candidate to power a chip that can be embedded in the body. Perhaps equally as important, the gentle sound waves also support versatility. A Swiss army knife of implantable devices, the chip can change its function to fulfill different biological needs. Its various modes are controlled by the same thing that fuels it. “Ultrasound is both a power source and a way to communicate with the device,” says Arbabian.

A tiny module, called a harvester, sits on the chip and converts ultrasound waves into electrical energy. By beaming pulses of ultrasound to the chip, Arbabian can send

encoded commands, like Morse code. “We can, for example, instruct it to start monitoring a certain parameter, like blood pressure, or channel an electrical pulse to stimulate a nerve or trigger the precise release of a drug at a particular location.”

The goal, he says, is to create an active “smart” chip or a distributed network of smart chips to not only execute specific commands, but also to monitor physiological parameters and transmit useful data about the patient. This information, on such things as insulin levels or blood pressure, is sent to an external device, where doctors can access it. In that vein, Arbabian and his lab team are working toward a closed-loop system in which the implant is self-sustaining and can run seamlessly in the body, without constant instruction.

In a closed-loop system, the chip’s sensors would trigger the release of a dose of its therapeutic agent, which could be an electrical pulse or a drug enclosed in a separate chamber of the chip. In patients with hypertension, for instance, the implant would monitor the arteries. If the chip sensed increased blood pressure, it would administer a drug to help bring the pressure down.

“We could see this system working for maintaining blood pressure, or managing urinary incontinence or diabetes,” says Arbabian.

He and his team are working on the next generation of the implant and partnering with other labs to test their setup in animals. They even have a research collaboration with the FDA, which is independently investigating the prototypes.

“There’s a lot more work to be done,” Arbabian says. “But there’s a lot of reason to be hopeful.” **SM**

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FEATURE

A toxic lifesaver, reconstructed

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When he landed in Cleveland as a freshman at Case Western Reserve University, he got a job working the night shift in a lab. He never really left one again. No one was more surprised than he when he discovered he liked working in a lab — a lot.

“I never even knew that things like labs existed,” he says. “I started learning about what went on in a lab and thought, ‘Wow, people get paid to do this stuff?’”

Early on, Ricci found his niche in advancing the understanding of the molecular workings of the hard-to-access and little understood world of the inner ear. Ricci, fascinated by how hearing works, has become an expert in mechanotransduction, the process by which mechanical sound waves from the outside world pass through the inner ear and are converted into electrical signals sent to the brain so we can hear.

That “aha” moment in New Orleans came from his deep understanding of hearing and the role played by ion channels that open only in response to sound vibrations.

The key cells in the hearing process — known as hair cells because hairlike cilia protrude from them — are hidden deep inside the inner ear in the bony, snail-shaped cochlea. Mammals have a limited number of the cells, and when the cells die off — whether from being damaged or destroyed by loud noises, simple aging or, in this case, a toxic antibiotic — the result is irreversible hearing loss.

The ion channels exist within the membranes of these hair cells. They are proteins that act as pores in the cell membranes and allow selective passing of potassium, sodium and calcium ions, which is how electrical currents pass in and out of a cell.

Ricci discovered that these pores, which open into tunnel-like channels, are bigger than the scientific community previously thought. Rather than measuring 0.8 nanometers, the pores are wider — measuring 1.3 nanometers across. Before his discovery, scientists believed that aminoglycosides worked like corks plugging up these channels. But, in fact, his research indicates that the drug molecules easily pass through the channels, streaming right into the cells.

Exactly how aminoglycosides destroy hair cells once they get inside remains a matter for speculation, but rather than solve this quandary, Ricci came up with this new idea: Why not just make the drug molecules too big to

enter through the channels in the first place, keeping hair cells safe and preventing hearing loss?

“To me, what’s cool about this approach is it shows how very fundamental basic science research can actually translate into helping patients,” he says. “This idea came from doing biophysical characterization of an ion channel. You don’t get much more basic than that.”

It took a few years before Ricci got to work on his idea because he had to deal with the loss of his home and his livelihood in the aftermath of Hurricane Katrina. He eventually made his way, with his family, to Stanford. His idea continued to brew until about 2008, when he approached Cheng, associate professor of otolaryngology, at a staff meeting. Cheng had recently come to Stanford from the University of Washington, where he had been studying aminoglycosides. When Ricci brought up his idea of creating a new version of an aminoglycoside that retained its antimicrobial powers, but didn’t cause hearing loss, Cheng was drawn in.

As a physician-scientist who treats children with hearing loss, Cheng knows firsthand about both the lifesaving properties of aminoglycosides and their toxic side effects. So he was quick to get involved.

“When a drug causes hearing loss it is devastating, and it’s especially disturbing when this happens to a young child, as they rely on hearing to acquire speech,” Cheng says. Despite this, aminoglycosides remain the “go to” drug for treating life-threatening infections, a choice made by many physicians worldwide.

“I was skeptical in the beginning,” Cheng says. But after a decade of partnering with Ricci, and building a team of drug development experts, they have now designed three versions of aminoglycosides that, in studies in mice, kill off bacterial diseases without causing hearing loss.

Designing a drug is difficult, especially for two basic scientists with no experience in that arena. So, when Ricci and Cheng first set out, they recruited help from experts both on and off campus. In 2013, they connected with SPARK, a program at Stanford that assists scientists in drug development and in moving

their discoveries from the lab into patient care. SPARK helped them create a team capable of designing a new drug, consisting of chemists, microbiologists, crystallographers, FDA advisers and more.

“From its inception the work has involved a broad team of investigators, both basic scientists and clinician scientists,” Ricci says. They recruited chemists like Robert Greenhouse, PhD, adjunct professor for otolaryngology, to help figure out how to change the shape of the compound. Ludmila Alexandrova, a research associate at Stanford, developed a mass spectroscopy assay for aminoglycoside detection. They also recruited clinicians such as Markus Huth, MD, a former postdoctoral scholar in Ricci’s lab, who conducted the first ototoxic testing of the new drug compounds.

More recently, the team has worked with crystallographer Hasan DeMirci, PhD, a research associate at the SLAC National Accelerator Laboratory, whose expertise has helped reveal the intricacies of how aminoglycosides interact with ribosomes, the site of protein synthesis in the cells of bacteria. Newer team members Mary O’Sullivan, PhD, a postdoctoral scholar, and Randy Lin, an undergraduate, are working in Ricci’s lab to help characterize the newly made compounds.

“We needed SPARK to tell us to go ahead and try all this,” Ricci says.

So far, they have completed two rounds of testing on 18 new antibiotic compounds. Of the 18 versions, three successful candidates have emerged for further study.

“During the first round, we were successful at creating drugs that don’t enter the ion channels and don’t kill hair cells,” Ricci says. “With the second round, we made significant progress at keeping more of the drug’s antimicrobial properties intact.”

Still, the three drug candidates are not as effective at killing off a wide range of bacteria as the researchers need for a final product, Ricci says.

The team is preparing for a third round of compound testing. To reach the level where the drugs could be tested in humans, they plan to first move testing into guinea pigs, a larger animal model

that more closely resembles humans.

“I think this next round is going to be a big leap in the quality of drug we develop,” Ricci says. “With every round we do, we’re doing the synthesis side much faster, with more knowledge, and things are really speeding up,” he says.

As a basic scientist who remains passionate about his ongoing work in the lab, Ricci says his foray into the foreign world of drug design has proved “super hard and frustrating.”

“Figuring out drug design is a nightmare even when there are people who know what they’re doing helping you along,” Ricci says. “I felt like I was back in grad school learning a whole new set of skills.”

But it’s a journey he’s fully committed to completing alongside Cheng and the rest of the team to produce a new set of lifesaving antibiotics that won’t cause hearing loss.

“It’s not always possible to see your basic science research make a difference in people’s lives,” Ricci says. “It’s nice to be able to give back a little — at least, I hope we can.” **SM**

— *Contact Tracie White at traciew@stanford.edu*

FEATURE Hear and now

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communication for people with hearing loss. Yotopoulos and her colleagues had organized the conference to increase awareness of the prevalence and risks of untreated hearing loss, and of the need to think about hearing in the context of accessibility for all ages and in all settings. “It’s such an important piece of what Stanford University is doing with education and with creating community,” Yotopoulos says. “If we aren’t able to hear and listen to each other, we don’t have anything.”

Participants at the conference looked at many aspects of hearing, such as how acoustics in public spaces could be enhanced; how hearing tests could be improved; how hearing aid device technology, service, and cost could be transformed for the better; and how close scientists

are to a cure. Even as they underscored the coming crisis of hearing loss in a ballooning population of aging adults, they envisioned a world designed to enhance listening and communication.

Yotopoulos had already seen, personally, the impact of some of these changes. In 2015, her father was fitted with two Bluetooth-enabled hearing aids at a Veterans Affairs clinic in Washington. “The audiologist was great,” says Lutz. “He said, ‘Now you’ve got hearing aids, Ed, but you know you’ve still got to learn how to listen.’ And my wife thought that was really great advice.”

Lutz has his own advice for people with hearing loss: “Don’t give up if the first pair of hearing aids doesn’t feel right. Let your mind get accustomed to the new sounds.”

He’s happy to hear the birds easily again. And he’s able to keep up with the clues when he and his wife watch their favorite mysteries.

“My wife can set the TV volume to what’s comfortable for her, and with the device I can set it for what’s comfortable for me,” says Lutz. “And I’m not afraid to go to a restaurant or a crowded place because I can adjust the ambient noise. I feel more comfortable around people in conversations, and I understand the kids better.”

Being able to communicate easily with his wife has been the most meaningful improvement. “Just being able to hear what she said, rather than having to have her repeat herself three times,” says Lutz. “Now I can hear her more often and I can answer her, so it’s clear, yeah, I’m paying attention to you. We have a pretty good life, but the hearing aids have enhanced it.”

Though they live far apart, Yotopoulos loves talking with her dad on the phone about everything from the activities of her now-teenage kids to the Lutzes’ latest adventures — such as learning to play the guitar and speak Spanish. It’s not only easier for her to communicate with him, but it’s also good to see him as the active, involved person he really is. “Having the hearing aids that actually work for him changed so much,” she says. **SM**

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FEATURE

Q&A

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instrument. The actual playing of an instrument improves auditory processing. Kids are able to do better in school. They can focus better.

COSTELLO: When you travel doing concerts now, you’re also meeting with biomedical researchers, like here at Stanford. What do you want to leave behind?

FLEMING: Only one thing: my interest in their work. I want to serve and spread their work. I can’t really teach them anything. They can teach me. **SM**

This interview was condensed and edited by Paul Costello.

FEATURE

All ears

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for the need for our listening devices to respond to mental health emergencies.

This got the attention of Adam Miner, PsyD, a Stanford behavioral AI researcher and an instructor in psychiatry and behavioral sciences. He began thinking about how “chatbots” — software programs that mimic a conversational partner — could make a difference in improving mental health. One of his observations was a little surprising: that the nonhumanness of chatbots was the very thing that could make them more effective than human counselors in some aspects of cognitive behavioral therapy, a type of therapy consisting of structured conversations aimed at teaching people skills to modify dysfunctional thinking and behaviors.

In an editorial in *JAMA* published Oct. 3, 2017, Miner cited several studies that showed people often spoke more openly about problems to nonhuman than human listeners. Why? Chatbots don’t judge or gossip. They won’t share sensitive information with an employer or a parent. (This is especially important with stigmatized conditions such as post-traumatic stress disorder.) And chatbots are available 24/7 for patients.

With one in six U.S. adults suffering from some form of mental illness, Miner is enthusiastic about using this technology to help people who lack access to mental-health professionals or health insurance.

He is focused on researching best practices to help developers build evidence-based online mental health services designed with underserved communities in mind.

One of the first mental health chatbots to be tested in a randomized, controlled trial is the Woebot, a text-based coach designed to improve the mood of college students who have anxiety and depression. Results from this small Stanford study, published in *JMIR Mental Health* in 2017 and led by Kathleen Fitzpatrick, PhD, then a clinical assistant professor of child and adolescent psychiatry, suggest that Woebot significantly reduced students' symptoms of depression over the study period.

"While mental health chatbots will never replace human therapists, there are simply not enough mental health professionals to meet the current demand," says Alison Darcy, PhD, adjunct professor of psychology, who founded Woebot Labs to develop and market this technology. "This approach is nowhere near perfect, but it's a start."

AUTISM DIAGNOSIS ONLINE

Autism spectrum disorder affects one in 68 children in the United States, yet the standard diagnostic process is complex, time-consuming and dependent on expensive specialists. This has resulted in diagnostic delays of 14 months on average and missed opportunities for early interventions.

There are no biological markers for autism — no blood tests or brain scans — so a definitive diagnosis relies on the identification of abnormalities in speech and behaviors. A full clinical evaluation involves a two-hour observational exam conducted by a trained specialist, followed by visits with a developmental pediatrician and/or psychiatrist. The process often takes days and thousands of dollars.

Dennis Wall, PhD, associate professor of pediatrics and of biomedical data sciences, wants to ease this access-to-care bottleneck by establishing a simpler set of speech and behavioral markers that can be identified by nonprofessionals in a short home video. In a new study published in *bioRxiv*, crowd-sourced evaluators — people with no clinical training — correctly identified diagnostic features of autism with 76 percent to 86 percent accuracy, simply by

watching a three-minute video and answering 30 questions about observed behaviors.

Wall's team continues to develop a faster, better diagnostic exam by using machine-learning technologies. These iterative software algorithms process streams of relevant data from children with and without autism (this could include voice, visual and exam data) to learn which behaviors are the most relevant to diagnosis. The more patients the software evaluates, the smarter and more accurate its diagnostic recommendations will become.

"I'm excited to begin using these AI technologies to help children with autism and their families around the world. We're only scratching the surface right now," says Wall, who recently completed a pilot study in Bangladesh.

Wall's spinoff company, Cognoa, is working with the Food and Drug Administration and clinicians to validate its diagnostic software for wider use.

SOCIAL MEDIA LISTENERS

Across the vastness of the Internet, there are countless disease support groups where ill people share questions, advice and hope. Nigam Shah, PhD, assistant director of Stanford's Center for Biomedical Informatics Research, is developing software that "listens" to these online conversations and monitors the effects of medical drugs after they have been licensed for use. The goal is to identify unreported adverse reactions.

To test the potential of this software, Shah and his lab teamed up with Brian Loew, CEO of Inspire health communities, and Kavita Sarin, MD, PhD, assistant professor of dermatology, to extract and analyze mentions of skin problems among 8 million online discussions posted by people taking erlotinib. The drug is used to treat several types of cancer, including non-small-cell lung cancer and pancreatic cancer. One of the challenges in this type of analysis is extracting relevant data from social media conversations, which are often nontechnical and context-dependent, and finding links between drugs and side effects.

Using text-mining and deep-learning software algorithms, the researchers not

only recognized known skin problems an average of seven months in advance of published clinical reports, but they also identified an undetected, rare, adverse drug effect — diminished sweating, also known as hypohidrosis. These results were published March 1 in *JAMA*, and this proof-of-principle study demonstrated that machine listening within online health forums can be used to improve health outcomes and reduce the societal costs of drug side effects.

CHALLENGES AHEAD

Entering the brave, new world of artificial intelligence-based listening will raise ethical, legal and social challenges. How do we protect the privacy of the patients whose data is collected and disseminated by the listening devices? How can we make sure that the software algorithms used to assist physicians in health care decisions are free from bias? Who is legally at fault if the use of one of these applications results in a serious medical mistake?

One initiative focused on working through these complex issues began with a Stanford-led project called the One Hundred Year Study on Artificial Intelligence. Through this effort, working groups of experts on artificial intelligence from around the globe will produce a detailed report on the impact of AI on society every several years for the next century.

The first report (<https://ai100.stanford.edu/2016-report>) was published in September 2016, and its health care section emphasized both the promise and challenges that we currently face: "AI-based applications could improve health outcomes and quality of life for millions of people in the coming years — but only if they gain the trust of doctors, nurses and patients, and if policy, regulatory and commercial obstacles are removed." **SM**

— Contact Kris Newby at krisn@stanford.edu

FEATURE

To hear again

CONTINUED FROM PAGE 31
telling each other, and not how the organ is working as a whole, which is what we had been doing for many years."

A decade ago, measuring such complex and extensive information would have been impossible, but technological advances enable researchers to separate individual cells and measure their transcriptome — that small percentage of the genetic code that is transcribed into RNA molecules. By studying transcriptomes, researchers hope to determine when and where genes are turned on or off in various types of cells and tissues.

“Technology has really turned the tables for us,” Heller says.

About six years ago, Heller’s lab adopted a technique, called single cell transcriptome analysis, invented in part in the lab of Stephen Quake, PhD, a professor of bioengineering and of applied physics. The process uses high-tech tools to decode the genetic instructions that enable cells to differentiate into other cells.

“We are analyzing all the genes expressed in individual cells during regeneration,” Heller says. “We just published a paper describing how the chicken utilizes two parallel regenerative processes. We need to figure them out, how they change over time. The cells are mixed up together and when we isolate the cells, we lose critical information, such as their precise location in the organ. Currently there are no informatics tools that allow us to reconstruct that so we’re creating our own.”

Heller’s lab has been hosting bioinformatics experts who are working on algorithms to describe how individual cells respond to regenerative or developmental triggers, and how they make decisions to develop into different mature cell types.

“We have really had to focus on generating the right tools with the intent of applying this technology, which I think is going to revolutionize the whole field,” Heller says. “We also plan to eventually apply this to our stem cell work.”

Heller is cautiously optimistic about the ability to develop hearing loss treatments. Work in genetic therapy and drug development to protect against the hearing loss side effects of aminoglycosides, a widely prescribed class of antibiotics, may be a bit closer to fruition, he says. But in general, inner ear hair cell researchers are in this for the long haul.

“In this field, there is no magical cure,” Heller says. “It will be a process. For example, if we discover that ‘trigger’ in chickens and fix it in mammals, we may be able to trigger something like an imperfect regeneration of hair cells in humans. It might not be a perfect fix. It might not fully cure deafness. But it may turn a hard-of-hearing person into a better-hearing person. That is the first step we have to take.” **SM**

— Contact Tracie White at traciew@stanford.edu

PLUS

Are you my doctor?

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Michigan aimed at bringing more of these stories to light and normalizing disability across the medical profession.

As a physician with a visible difference, there are many days I am personally impacted by this — some good, some bad, all interesting. This often becomes dinner table conversation for me and my husband, who also has a disability. We have discussed a concept that I believe rings true for all physicians who have a defining characteristic that sets them apart and puts them at risk for being profiled negatively: invisible → visible → invisible.

People with disabilities used to be invisible, a result of lack of public access and very high societal stigma. As the disability rights movement progressed and key legislation was enacted to define our rights, we became more visible in society. It would be ideal,

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however, to again be invisible, but in a much more empowered way. This new form of invisible would be one in which access is so ubiquitous and stigma so low that entering a patient room would not turn heads or even elicit a response. People with disabilities would, in fact, not stand out in the profession, but would rather be a common sight in all health care environments.

It is time we recognize that the human condition is not perfect. Our profession must continue to strive to mirror the population we serve and to normalize disability, as well as all differences — both visible and invisible. By doing so, patients and providers alike would feel more welcomed and valued, and be the better for it. **SM**

UNSILENCED

A YOUNG WOMAN FINDS HER VOICE

Nineteen-year-old Alyssa Davilla has things to say. Until recently, no one knew. Davilla, who was born missing a large region of chromosome 5, voices only a handful of words. Her gene defect produces profound neurological challenges, including seizures and autismlike symptoms, which hampers her ability to speak. Medical problems such as aspiration pneumonia have led to frequent stays at Lucile Packard Children's Hospital Stanford; she's monitored by several of the hospital's physicians.

For years, Davilla's parents, Monique Davilla and Matt Volkman, had few tools to communicate with her. She could say "food" and "water." She could point to cards that said "Yes," "No," "Want more," "All done" and "Want to play a game." Beyond this tiny vocabulary, the family used a lot of guesswork.

Then, in May 2017, Monique Davilla heard about a speech therapist who focuses on patients with severe communication impairments. Her daughter had worked with other speech therapists, but this one was different.

"The first time Ali met Alyssa, she was able to tell me that Alyssa can spell," Monique Davilla says. "I had no idea."

The speech therapist, Ali Steers, who is in private practice in the Los Angeles area, helped Alyssa Davilla use an iPad application to augment her communication. A version of the Compass app organizes a large vocabulary

into practical categories; users tap words and pictures to create phrases that are spoken by a recorded voice.

The use of the app has revealed surprises about Alyssa Davilla. This winter, when she had a cold, she could say that her head ached; she'd never expressed pain before. For the first time, she's showing a sense of humor, sometimes deliberately answering questions wrong, then waiting, smiling, to see if anyone realizes she's being silly.

"More and more, we're seeing her personality come out," her mother says. "I thought she was shy. She's not; she's actually pretty social, but she didn't have a way of communicating."

And she really wants to connect. On a recent afternoon, Alyssa Davilla met a visitor at the door of her family's home in San Jose, California, holding a favorite jigsaw puzzle. "Fi, fi" she said, pointing to the fish on the puzzle. In her home-school classroom, her longtime teacher chatted with her

about what clothing to wear in different weather conditions. Via the app, she picked a blouse, pants and sneakers for a sunny day; a sweater, jeans and rain boots for rainy weather. She's learning arithmetic, spelling and grammar. Her family hopes she'll learn to write her thoughts and needs.

The app also helps make social connections: Questions about her gregarious dog used to fall to her mom, but now, Alyssa Davilla can play a recording that says, "I have a service dog and his name is Elmo." She can tell people her favorite TV shows — *Dora the Explorer* and *Blue's Clues* — or say if she wants space. During a recent hospital stay, when there was too much hustle-bustle in her room, she told the nurses, "I'm sick, I need to rest."

How does it make her feel to be able to communicate this way? "Good, awesome, smart."

After years of believing that her daughter's ability to converse would always be limited, Monique Davilla is delighted by the change. "I'm so grateful," she says. "I was told by so many speech therapists that my daughter didn't have the cognitive awareness to communicate like this." — ERIN DIGITALE



Alyssa Davilla uses an iPad app to communicate by selecting words and phrases she wants to express. Her dog, Elmo, licks her feet to relax her as she talks with visitors.

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Worry weight

STRESS AT THE WRONG TIME CAUSES FAT CELLS TO FLOURISH

Get a good night's sleep if you want to avoid gaining weight. That's one lesson from new Stanford research on what spurs the development of fat cells. The scientists found that your legions of precursor fat cells are more likely to turn into actual fat if your body's levels of glucocorticoids — mainly the "stress hormone" cortisol — rise at night. The same applies if your sleep patterns are interrupted or if you take nighttime doses of glucocorticoid drugs, which are used to treat rheumatoid arthritis, among other diseases.

The research suggests weight gain could be controlled by regulating the timing of pulses of glucocorticoid hormones, says Mary Teruel, PhD, assistant professor of chemical and systems biology and senior author of the study published April 3 in *Cell Metabolism*.

Researchers have long known that glucocorticoids trigger precursor cells to convert to fat cells, and that our fat tissue contains a huge excess of precursor cells that can convert, given the right signals. They've also known that at certain times of day our bodies are awash with glucocorticoids. Normally a person's levels of glucocorticoids rise and fall in a 24-hour cycle, peaking around 8 a.m., dropping to their lowest around 3 a.m. the next day, and then rising to their peak again about five hours later.

Hence Teruel's puzzlement: "Why aren't we drowning in fat every time glucocorticoid levels go high in the morning? And why is losing the normal rhythm of glucocorticoid secretion

— such as in conditions of chronic stress, jet-lag and sleep disruption in shiftworkers — so linked to obesity?"

Teruel's team's research has an answer: Fat-cell maturation ramps up if the trough in stress-hormone exposure lasts less than 12 hours — for example if you are up at midnight worrying. Chronic exposure also gets fat cells going. However, short bursts of the hormones during the day don't have an impact.

"Our results suggest that even if you get significantly stressed or treat your rheumatoid arthritis with glucocorticoids, you won't gain weight, as long as stress or glucocorticoid treatment happens only during the day," Teruel says. "But if you experience chronic, continuous stress or take glucocorticoids at night, the resulting loss of normal circadian glucocorticoid oscillations will result in significant weight gain."

— ROSANNE SPECTOR



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