**Procedure could benefit more stroke patients**

By Bruce Goldman

A 38-year-old woman who was diagnosed with a rare eye disease "nearby of a rare eye disease. It's really surprising to see that the link works through a very classical learning mechanism," said the study's lead author, Lang Chen, PhD, the study's lead author and a postdoctoral scholar in psychiatry and behavioral sciences. "Based on our data, the unique contribution of positive attitude to math achievement is as large as the contribution from IQ." The scientists had not expected the contribution of attitude to be so large, said the study's senior author, Vinod Menon, PhD.

**Studying how chronic disease can lead to poor bone health, with an eye toward therapies**

By Erin Digitale

Kyla Kent had just finished conducting CT scans of bones in a 10-year-old boy's forearm and lower leg. Walking him back to the waiting room, she asked how he wanted to explain the images to his mom.

The detailed view provided by the CT machine, a high-resolution peripheral quantitative computed tomography scanner called XtremeCT II, is giving Stanford scientists unusually precise information about the tell of chronic diseases on children's bones. But young research participants are often more excited about the images' gee-whiz factor. Kent could sense the boy's mental wheels turning. "Mom, here's what happened," he said. "From a single cell, a very small wizard was born. And he goes inside my arm — it doesn't hurt, I just felt a little pain — and while he's there, he takes a picture of the inside..."
Researchers find sleep improves with aid of incontinence drug

By Hanae Armitage

A drug used to curtail episodes of urinary incontinence in women also improves quality of sleep, a re-

searcher at the School of Medicine reports.

People who experience urinary incontinence, espe-
cially at night, often have trouble maintaining normal sleep cycles. Now, the Stanford researcher sees promise in using one drug to help remedy both problems.

“Two of the biggest-quality-of-life factors for older women are poor sleep quality and incontinence, and the older you get, the more prevalent both conditions are, and they do seem to be correlated,” said Leslee Subak, MD, professor and chair of obstetrics and gynecology. “And so, if we can find a drug to treat one and effectively decrease the other, that could be big for improving quality of life.”

A paper describing the study was published Jan. 11 in Obstetrics & Gynecology. Subak is the senior author, Quaratul Ann Warsi, MD, a former clinical research scholar at the University of California-San Francisco, is the lead author.

In 2012, Subak, who was then on the faculty of UC SF, and her colleagues conducted a study called Bringing Simple Urge Incontinence Diagnosis and Treatment to Providers, or BRIDGES, which analyzed a specific drug’s around-the-clock efficacy in curbing urgency incontinence, a condition characterized by a sudden urge to urinate and sometimes accidental leak-
age. The researchers conducted the study in women, as urgency incontinence is five to 10 times more common in women than it is in men.

The drug, fesoterodine, decreased accidental urina-

tion in study participants. The researchers also observed that it produced a handful of secondary beneficial ef-

fects, including less nighttime wakefulness caused by an urge to urinate.

Given the drug’s success in diminishing urgency in-

continence, including while sleeping, Subak followed up with a new question: Could this drug simultane-
ously help women catch extra shut-eye? Self-reported data from 645 female participants indicated that the answer was yes.

Two birds with one drug

In the initial 12-week BRIDGES study, Subak and her team recruited 645 female participants from 3 sites in the United States, whose average age was 56, and used a standardized evaluation of urgency incontinence to determine which participants would be best-suited for the trial. To qualify, participants had to indicate that they had experienced problems over the previous three months with accidental urination, occurring with a sudden urge to urinate.

Fesoterodine belongs to a larger class of drugs known as antimuscarinics. These agents help control acciden-
tal urination by blocking receptors in the bladder that, when activated, tell it to contract, a key physiological part of urination.

To determine if the drug also improved sleep qual-
y, the researchers gave participants a standardized sleep evaluation, called the Pittsburgh Sleep Quality Index. The self-reported evaluation measures seven sleep-associated aspects, such as sleep duration, difficulty falling asleep and how long it takes for an individual to fall asleep. Each category is scored on a scale from 0-3; at the score is tallied — the higher the score, the poorer the sleep quality. According to the Pittsburgh Sleep Quality Index, a score of 5 or more indicates poor sleep, and for the 57 percent of the cohort who reported poor sleep, the average score was 6.4.

Women in the study recorded their baseline sleep patterns, the majority reporting that they were getting up one to two times per night. Those numbers may not seem bad on paper, but Subak said dis-
rupting the sleep cycle more than once every night can start to take a toll.

“Getting up one time per night is acceptable for most people, but twice really starts to be disruptive and is associated with poorer quality of life and more day-
time sleepiness,” Subak said.

Women in the study who took the drug reported better sleep: Instead of having to empty their bladder once or twice a night, the group, on average, reported emptying only once or not at all. Subak pointed out that finding a drug that can simultaneously ad-
dress incontinence and poor sleep is crucial for women who experience both, she said. “As age increases, so do the prevalence and frequency of nighttime urination, and that especially poses risks for someone who is older,” Subak said.

Thinking holistically

About a quarter of reproductive-age women, about half of menopausal women and about 80 percent of women who are 80 and older experience urgency in-
continence. The older a woman is, the more dramatic the effect incontinence has on her quality of life.

Subak recalls a patient from the study telling her that incontinence doesn’t kill you, but it takes your life away. “Patients might end up secluding themselves espe-
cially because they’re worried about their bladder,” she said. “But far worse, urinary incontinence is also one of the biggest factors for falling and fracturing for older women, especially those who have osteoporosis. That’s why addressing 24-hour incontinence, especially in the geriatric population, is so critical. Drugs such as fesoterodine empower physicians to think through the most well-rounded treatments for patients, Subak said, and there are many other similar pharmacological options that could work in the same way, too.

“It’s a reminder to us as physicians to look at many co-morbid conditions that are synergistic. If an older person is saying ‘I’m having trouble sleeping,’ ask about nighttime urination; ask about urgency incontinence,” Subak said. “It’s important to look holistically at a pa-

tient’s sleep and elder care. Many who have many of these problems co-exist. We have an opportunity to really look at how treating one can improve the others too.”

Subak is a member of the Stanford Child Health Re-

search Institute.

Researchers at the University of Utah, UC SF, Univer-

sity of Pennsylvania, University of Alabama-Birming-
ham, University of Iowa, University of Texas-Austin, Brown University, University of Tennessee Health Sci-

cences Center, Harvard Medical School, Oregon Health Sciences University, University of Texas Health Science Center at San Antonio and California Pacific Medical Center Research Institute also contributed to the work.

The study was funded by an investigator-initiated award from Pfizer Inc. and by the National Institutes of Health.

Stanford’s Department of Obstetrics and Gynecol-

ogy also supported the work.
Weight flux alters molecular profile of body systems, study says

By Hanae Armitage

The human body undergoes dramatic changes during even short periods of weight gain and loss, according to a study led by researchers at the School of Medicine. As people pack on pounds or shed excess weight, they exhibit notable changes in their microbiome, cardiovascular system, immune system and levels of gene expression, the study found.

The researchers integrated a slew of “omics” profiling techniques to gather heaps of data revealing unique details of different participants’ genomic, molecular, metabolic and bacterial composition. “Omics” is equivalent to tacking “the study of” to the names of areas of biological inquiry. For example, “genomics” roughly translates to “the study of genes,” and “proteomics” to “the study of proteins.”

A paper describing the work was published online Jan. 17 in Cell Systems. The lead authors are Stanford postdoctoral scholars Wenyu Zhou, PhD, and Hannes Röss, PhD; staff scientist Kevin Cool, PhD; and former postdoc- toral scholar Brian Piening, PhD. Senior authorship is shared by Michael Snyder, PhD, professor of genetics at Stanford; Tracey McLaughlin, MD, professor of medicine at Stanford; and George Wein stock, PhD, professor and director of medical microbiology and immuno- natory, an independent, nonprofit bio medical research institute.

“The goal here was to characterize what happens during weight gain and loss at a level that no one has ever done before,” Snyder said. “We also really wanted to learn how prebiotic diets might differ in terms of their personal omics profiles and their molecular re- sponse to weight fluctuations.”

Snyder and his colleagues found that even a modest weight gain — about 6 pounds — the human body changed in dramatic ways at the molecular level. Bacterial populations morphed, immune responses and inflammation flared, and molecular pathways associated with heart disease were activated. “But that’s not the end of the story. When study participants lost the weight, most of the rest of the body’s systems went back to their original states, the study found.

Snyder’s lab has a particular interest in understanding weight change on the microscale among people who are insulin resistant, meaning their glucose-process ing ability is compromised, because it’s a common precursor to Type 2 diabetes. To that end, the study compared differences in baseline omics of insulin-resis tant participants with those of healthy individuals. The researchers then looked at two major questions: How does weight gain affect omics profiles, and what happens once that weight is lost?

‘Billions of measurements’

The study included 23 participants. Thirteen were insulin-resistant, and 10 were insulin-sensitive, or able to process insulin normally. The participants had been on diets with the same caloric intake for 25 and 35 kilograms per square meter. (A BMI of 25 is on the high-end of normal; a BMI of 30 roughly equates to morbid obesity.)

The researchers pooled information from each person’s transcriptome, a collection of molecules that reveal patterns of DNA expression; proteome, the complete set of proteins an individual actively produces; microbiome; and genome. “In the end, we literally made billions of measurements,” said Snyder, who is the Stanford W. W.Talkman, MD, FACS, Professor in Genetics.

At the outset of the study, Snyder and his team found notable baseline differences between the insulin-resistant and insulin-sensitive groups. Among disparities in protein production and metabolism, more than 4000 microbial populations, Snyder spotted one big discrepancy: Molecular mark ers for inflammation were only found in the bloodstream of insulin-resistant participants. Inflammation is a known issue in people with diabetes, and early omics profiling like this, Snyder said, could help flag inflammation-associated molecules in people who are not diabetic but at risk for the disease.

“In these analyses, we’re looking at what molecules are changing, and then we’re expanding them to the pathway level,” Snyder said. “The pathway level is equivalent to a system, like the immune or cardiovascular system. “So, when we find a molecule that seems out of whack, we then ask if it falls into any larger pathways in the body.”

After looking for differences at baseline, the researchers changed up the pa rameters. The participants had a high-calorie diet, and after 30 days they had, on average, tacked on 6 pounds. And with weight gain — moderate though it was — omics profiles shifted too. Inflammation markers went up in both the insulin-resistant and healthy groups. In insulin-sensitive participants, a microbial population called Akkermansia muciniphila, which is known to protect against insulin resistance, shot up.

But perhaps the most striking change was a shift in gene expression associated with increased risk for a type of heart failure called dilated cardiomyopathy, in which the heart cannot pump blood effi ciently to the rest of the body, Snyder said. “That was quite surprising. I didn’t expect 30 days of overeating to change the whole heart pathway,” he said. “But this all fits with how we think of the human body — it’s a whole system, not just a few isolated components, so there are systemwide changes when people gain weight.”

But Snyder said not to sweat the holiday feast just yet; there’s good news too. Once the participants had dropped the excess weight, their microbes, molecules and gene-expression levels bounced back to their normal levels, for the most part.

Omnis in the future of medicine

However, a small subset of weight gain-associated shifts in protein and molecule production did persist, even after participants had shed the extra pounds, the study found. There’s not enough evidence to draw concrete clinical conclusions, “but it is an indication that some of these effects could be longer-lasting,” Snyder said. One thing to note, he continued, is that even though there were trends in omics shifts, each participant exhibited particular changes to his or her own specific omics profile — a nod to the importance of deep, in tegrative sequencing and data collection when diagnosing and treating patients with precision health tools.

“Big data will be critical to the future of medicine, and things like these integrative omics profiles will offer an understanding of how the human body responds, in a very personal way, to dif ferent challenges,” Snyder said. “It think it’s important for us to be managing hu man health in the future.”

The work is an example of Stanford Medicine’s focus on precision health care, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

The study’s other Stanford co-authors are postdoctoral scholars Guji Jui Gu, PhD, Trijwani Misra, PhD, Imon Banerjee, PhD, Colleen Craig, PhD, Reza Saini, PhD, Liang Liang, PhD, and Charles Abbott, PhD; research assistants Brian Tapan, PhD, and his team found notable baseline differences between the insulin-resistant and healthy groups. In insulin-sensitive participants, a microbial population called Akkermansia muciniphila, which is known to protect against insulin resistance, shot up.

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Three faculty members named National Academy of Inventors fellows

Three School of Medicine faculty members have been named fellows of the National Academy of Inventors. Fellows are selected based on their “innovation in creating or facilitating outstanding inventions that have made a tangible impact on quality of life, economic development and welfare of society,” according to the academy.

The Stanford fellows are:

Helen Blau, PhD, the Donald E. and Delia B. Baxter Foundation Professor and a professor of mi crobiology and immunology. She directs the Baxter Laboratory for Stem Cell Biology. Her research has uncovered regulatory networks controlling nuclear reprogramming and therapeutic agents to enhance muscle regeneration in aging and dystrophy.

STANLEY COHEN, MD, the Kwoh-Ting Li Pro fessor and professor of genetics. His research helped spawn the revolution in human genetic engineer ing. His lab currently studies mechanisms that affect the expression, decay of normal and abnormal mRNAs, and also RNA-related pathways that regulate microbial antibiotic resistance.

H. TOM SOH, PhD, professor of radiology and electrical engineering. He has devised sensors ca pable of continuously monitoring specific biomol ecules in vivo and a control system for achieving real-time, closed-loop controlled drug delivery in live animals.

The new members will be inducted in a ceremony on April 5 in Washington, DC.
On ranking drug companies’ clinical trial reporting

Pharmaceutical companies have come under fire in recent years for failing to meet standards for reporting the results of clinical trials, but a new analysis by the nonprofit organization Bioethics International indicates that some companies are improving. In December, Bioethics International published its second “Good Pharma Scorecard,” which found that companies are making “clear progress” on transparency in BMJ Open. The 2017 ranking evaluated clinical trial registration, results reporting, clinical study report synopsis sharing and journal article publication rates for new drugs approved by the Food and Drug Administration in 2014 that were sponsored by pharmaceutical companies. We found there are some emerging industry leaders that are clearly opportunities for other companies to do more.

1 Why is such a scorecard necessary?

MELLO: Disclosing complete information about clinical trials is important because it gives doctors, prescription drug formulary managers and others the information they need to make the best decisions concerning prescriptions and insurance coverage. Historically, not all trial results have been reported, creating a selective view of the evidence base for a drug. The National Institutes of Health policy now requires making information about all clinical trials available to alleviate public concerns about whether useful information is being hidden and speed up the decision-making process.

2 What are the main takeaways of this second scorecard?

MELLO: We found that companies are taking their legal obligations around clinical trial reporting seriously. There is high compliance with the reporting requirements of the federal FDA Amendments Act. We also found there are some emerging industry leaders that are going further than the law requires in getting patients and doctors the information they need — and there are clear opportunities for other companies to do more.

The 2017 scorecard shows progress within the industry on some measures since the first scorecard was released in 2015. We found that the proportion of new drugs for which all phase-2 and -3 trials that supported a new drug application were disclosed went up from 50 percent in the 2015 rankings to 67 percent this time. We also found that the public availability of results for trials conducted in patients for each drug went up from a median of 87 percent to 96 percent, measured at 13 months post-FDA approval.

3 How does the scorecard process work?

MELLO: For new drugs approved by the FDA in a given year that were sponsored by the largest 20 pharmaceutical companies, a team of researchers scour FDA documents, nearly 40 clinical trial registries and medical journal articles, and then they match up drugs, clinical trials and public reports. We conduct this analysis for each trial, then each drug and finally each company. We create a company ranking based on all the drugs each had approved that year. And we work independently of companies, but give them a chance to review our results and methods to make sure we haven’t missed anything.

4 Why are some companies scoring lower?

MELLO: There are a number of issues that may have contributed to this. One issue that is very much in the spotlight at the moment is the high cost of prescription drugs. But much of this distrust dates to incidents many years ago in which it was discovered that companies incompletely reported clinical trial information, or in some cases distorted published analyses, and the drugs were later linked to safety problems. Following the old adage that sunlight is the best disinfectant, the transparency movement has been an effort to restore the public’s confidence that pharmaceutical companies can conduct and report clinical research responsibly.

5 Polls routinely show that most Americans believe pharmaceutical companies are more concerned with profit than people. Is greater transparency about clinical trials likely to improve this situation?

MELLO: We conclude in our study, “Celebrating progress — and identifying where it is not occurring as quickly as it could — can move the field forward toward a shared vision of transparency and what it can achieve.”

The first scorecard showed that nearly half of all drugs reviewed by the FDA in 2012 had at least one phase-2 or -3 trial that was not published, and only 20 percent of final trial results were posted on the ClinicalTrials.gov registry that drug company helped spur the reporting improvements since then.

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Medical school news office wins national awards

By Susan Ipaktchian

Writers and editors in the School of Medicine’s Office of Communications and Public Affairs have received top awards for their work in the Association of American Medical Colleges annual competition. The office received a total of seven awards, including three golds in the contest’s writing categories, for work published in 2016-17. Science writer Krista Conger received the basic-science writing category for “Of mice, men and women,” an article by Krista Conger that won the science writing category for “Of mice, men and women,” an article by Krista Conger that won the science writing category for the magazine Science writer Krista Conger re-

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Pre-approved drugs used for treatment of rare eye disease

By Becky Bach

Demonstrating the potential of precision health, a team led by a researcher at the School of Medicine has matched existing drugs to rare eye proteins expressed by patients with a rare eye disease.

"Analyzing fluid samples from the eye can really change how we look at it," said Vinit Mahajan, MD, PhD, associate professor of ophthalmology.

The team employed proteomics, the large-scale study of proteins, to identify four on-the-market drugs that successfully quelled symptoms triggered by several of the proteins, matching each one with abnormal levels of immune-signaling molecules called cytokines and inflammatory compounds that could be treated with steroids, so the research team decided to put steroid implants into three of the NIV eye implants. The implants, which release steroids continuously over two years, reduced levels of 31 molecules related to inflammation and the eye's abnormal immune response.

In the study, the researchers eventually developed scarring around the implants, suggesting that some of the proteins contributing to inflammation weren’t effectively blocked even after the steroid implants, these eyes still expressed elevated levels of the inflammation-related protein interleukin-6.

"This constant uphill battle to save the vision of NIV patients is not going to end overnight," said Jeffrey Goldberg, MD, PhD, professor and chair of ophthalmology. "It's innovative, has broad applicability and, most importantly, is helping patients."

The researchers used this clue to solve another issue: Why did a patient's right eye remain attached in an NIV patient who had already lost the use of one eye? The drug took clodizumab to block interleukin-6 after reattaching her retina. The therapy was effective, marking the first time a retina has remained attached in an NIV patient and suggesting the drug may be helpful to others with similar scar tissue inside the eye, Mahajan said.

The researchers also used the protein analysis to supplement and confirm the classification of NIV into five stages of severity. Now, in addition to physical symptoms, they can now provide doctors with each stage, Mahajan said. For future patients, a liquid biopsy from the eye could help provide more precise diagnoses, he said.

More gradual decline in eye health

For the NIV patients in this family, the slope of their decline, once steep, is now more gradual. "We’re still working on a cure," Mahajan said. "But we can do a better job of trying to maintain their sight with what we’ve learned.”

The applications of the approach are even broader, Mahajan said.

"In the future, we can imagine, in difficult-to-diagnose, nos patients or patients not responding to treatment, just removing a few drops of fluid from the eye to very quickly learn exactly which proteins to target," he said. "Liquid eye biopsies are outpatient procedures that are safe and painless."

Mahajan said he believes the work illustrates the power of proteomics, which could help fulfill the potential of precision health to diagnose diseases before they advance and provide a real-time look at biochemical processes driving disease.

"This is a fantastic example of the precision health approach we’re taking in ophthalmology at Stanford," said Jeffrey Goldberg, MD, PhD, professor and chair of ophthalmology. "It’s innovative, has broad applicability and, most importantly, is helping patients."

Researchers at the University of Iowa and Columbia University also contributed to the study.

The project was funded by the National Institutes of Health; the Doris Duke Charitable Foundation; National Cancer Institute, Research to Prevent Blindness; the RD-Cure Consortium; the Tistou and Charlotte Kerstan Foundation; the Schneeweiss Stem Cell Fund; the Susan F. Hoffman Fund; and the Professor Gerdude Rostchild Stem Cell Foundation; and the Gribou Family Foundation.

Stanford’s Department of Ophthalmology also supported the work.

Iowa woman, family members live with rare eye condition

By Becky Bach

Darlene Katzin considers herself lucky. After all, she’s 74 and still has some sight, albeit limited, in her right eye.

Katzin is a member of what she calls “the blind family,” a large, multigenerational Iowa family affected by a rare eye disease known as neovascular inflammatory vitreoretinopathy, or NIV. The disease stems from a mutation in the calpain-5 gene, which codes for an enzyme that breaks down proteins in some cells in the retina.

Katzin’s mother went blind, as did her brother, cousins and dozens of other distant relatives. “I lived with blind people all my life. We knew what to expect,” said Katzin, who lives in a small southeastern Iowa town with her boyfriend, Ed, and her dog, Tigger.

She began wearing glasses at 14 and has suffered from so many complications along the way she's lost track. As her vision slipped away, Katzin lost her driver’s license and was forced to give up her job as a housekeeping manager in Pennsylvania and return to Iowa.

A correct diagnosis, at last

But she was never correctly diagnosed until she experienced a blinding hemorrhage more than a decade ago when she was in Iowa City for a college graduation.

“We went to eat at a sports bar, and I was looking at TV and all of a sudden it was gone. I told my friend, ‘My eye just hemorrhaged.’”

That emergency room visit, and the tests that followed, led to her diagnosis and her introduction to Vinit Mahajan, MD, PhD, who moved this year from the University of Iowa and is now an associate professor of ophthalmology at Stanford.

Katzin said she was glad to participate in his research, which she hopes will help others with conditions like hers.

It isn’t an easy condition to live with. Katzin said she misses being able to drive and the independence a driver’s license brings. “I don’t like being dependent,” she said, reflecting on the time it takes her friend to drive her to the eye clinic in Iowa City, or even to the local Walmart, where she tries to do all of her shopping to save trips.

But she’s eager to emphasize that her plight isn’t that bad.

When she bumps into people, she just explains that she’s blind and couldn’t see them. “I just laugh it off — it’s no big deal,” she said. She enjoys gardening and spending time with her dog and with family and friends.

“If you ask any of my blind relatives, life is good,” Katzin said. “Although we do not see, we still have our sense of humor. We still have our hearts of gold. We still enjoy life.”

Vinit Mahajan

Darlene Katzin (left) and several members of her family have an eye disease known as neovascular inflammatory vitreoretinopathy.

"This is a fantastic example of the precision health approach we’re taking in ophthalmology at Stanford."
The work, much of which focuses on kids, is led by Mary Leonard, MD, professor of pediatrics and of medicine and the center's founding director. Many chronic childhood diseases, including diabetes, chronic kidney disease, inflammatory bowel disease, congenital heart defects and childhood cancer, take a silent toll on patients' bones. Leonard and her team want to help patients maximize their bone health in childhood and reduce their risk for osteoporosis later on.

"A critical period"

"Childhood and adolescence is a critical period for building a big, strong, healthy skeleton," said Leonard, who holds the Alice and Pete Harman Professorship for the Chair of the Department of Pediatrics. Healthy children and teens have a unique opportunity to build a bulkwark of bone mass to prevent osteoporosis later in life, she said. Throughout childhood, and especially during the growth spurt of puberty, the bones are constantly being reshaped by the interplay of two types of bone cells: osteoclasts, which chew up existing bone, and osteoblasts, which build new bone and mineralize it with plenty of calcium and phosphorus. In healthy kids, many different physiological factors — including diet, weight-bearing exercise and the activity of various hormones — affect the bone-modeling process, shaping how big and heavy the bones become.

"The flip side of this is in chronic disease, we think there's a window during development when kids' bones are especially vulnerable," Leonard said. Chronic disease can hurt adults' bones, too, but for children who are supposed to be building enough bone to last a lifetime, the effects can be especially severe. "And once you stop growing, there's little opportunity to make the bones thicker," Leonard said. "That ship has sailed."

As experts at Lucile Packard Children's Hospital Stanford and other institutions develop new ways to help children survive previously life-shortening illnesses, long-term damage to kids' bones becomes more important to address. "We need to shift to focus health activities toward children as early as possible," Leonard said.

A powerful scanner

One key tool in Leonard's efforts to do that is the SAMBA Center's high-resolution CT scanner, the only such machine west of Missouri. It is designed to provide an extremely detailed view of the bone structure inside the arms and legs, and it uses much less radiation than a typical medical CT scanner.

"High-resolution CT scan help us understand why the bones are weak," Leonard said. "Is it because the shell of the bone is thin? Is it not dense enough? Does it have pores or holes it shouldn't have?" These details are telling: Inflammation leaves one type of damage traced on the bone, steroid medications leave another. Vitamin D deficiency looks different, too. "If we understand the underpinnings of the fragility, it gives us insight into the mechanism of bone damage," she said.

The high-resolution CT is such a new tool that the Stanford team had to begin by creating a normative database of bone scans from healthy children, a process that is still underway. They are also collaborating with other scientists around the world to agree on standardized methods for measurements.

Once the high-resolution CT data is collected, it's studied using finite element analysis, a technique borrowed from engineering physics. "We treat the bone like it's a bridge or airplane wing and see: What is the failure load?" Leonard said. "Two children with the same bone density may not have the same functional level of weakness in their bones; high-resolution CT can distinguish between them."

"We don't do these scans to predict fractures in children; we do it because we want to understand what their disease is doing. It helps us think more about different treatment options," Leonard said.

The team's work is an example of how Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and predict disease at an early stage.

The team is also using more traditional methods of assessing bone health, including dual X-ray absorptiometry, or DXA, scans, which provide information about children's overall bone mass, lean body mass and body composition, as well as hand-grip testing, leg-endurance testing and maximum force generation tests, which measure different elements of limb strength to allow the team to assess how bones and muscles function as a unit.

Putting bone discoveries to use

Bone health discoveries are already strengthening some patients' bones.

For instance, new medicines for inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis, now allow doctors to avoid treating kids with drugs that damage their bones. "These kids used to get treated with high doses of prednisone," Leonard said. "They had terrible skeletal fragmentation." The steroids led to vertebral compression fractures, injuries more typically seen in elderly osteoporosis patients. Now, doctors can instead prescribe biologics that selectively suppress gut inflammation and directly block the inflammatory molecules that damage bone.

Not only are the patients better off, the new treatments are helping researchers tease apart how much bone damage is caused by steroids and how much by the disease itself, which also damages bones. "Right now, the patients we're also scanning," said Leonard, "we want to strengthen their bones so they can be happier and more active in childhood and throughout their adult lives as well."

MIT’s Aviv Regev to present annual McCormick Lecture Feb. 1

Computational and systems biologist Aviv Regev, PhD, will give the annual McCormick Lecture on Feb. 1 at the Li Ka Shing Center for Learning and Knowledge. The title of her talk will be "Reconstructing circuits — the power of random." The event is free and open to members of the Stanford community. A reception will follow. The deadline to register is 7 p.m. Jan. 31.

A professor of biology at MIT, Regev is also a Howard Hughes Medical Institute (HHMI) Investigator, director of Klarman Cell Observatory at the Broad Institute and chair of the medical school's Institute for Systems Biology.

Regev and her colleagues employ experimental and computational approaches to decipher the mechanisms that underlie the transcriptional regulatory circuits in organisms ranging from yeast to humans. Members of her lab study how these transcriptional circuits change on a variety of time scales, from hours to millions of years. These studies yield detailed regulatory circuit wiring diagrams and principles that govern the emergence of novel functions in gene regulation.

The lecture is named for Katharine Dexter McCormick, a biologist and feminist who left a large bequest to Stanford with the hope that it would be used “in the furtherance of the study and teaching of School Medicine and more especially for the encouragement and assistance of women in pursuing the study of medicine, in teaching medicine and engaging in medical research.”

"I think it was very exciting to see how different their bone microarchitecture will be compared with the healthy controls we're also scanning," said Candice Sheldon, MD, a clinical fellow in pediatric nephrology who with Leonard is mentoring. Looking ahead

Chronic kidney disease patients tend to be shorter than average, Sheldon said. Although growth-hormone and vitamin D supplementation are already used to help promote growth and protect these patients' bones, they are still more likely to break bones than healthy kids. "We still haven't figured out how to optimize therapy so that these kids don't get as close to their healthy counterparts as possible," Sheldon said. She hopes the CT scans will give clues as to the exact mechanism of bone damage so they will put the team on the track of better therapies.

The team also hopes to understand how receiving a kidney transplant at a young age affects the child's bone growth. "Can we transplant this plant, how much do they recover? Packard Children's has the largest pediatric kidney transplantation program in the country and spearheaded the development of steroid-free immunosuppression regimens in children. This is the ideal place to determine if bone density, structure and strength can recover following kidney transplant in children and adolescents.

In the future, Leonard hopes to investigate the long-term impact on bones of a new form of bone-marrow transplantation being developed at Stanford for certain cancer patients. Radiation therapy that is traditionally used to prepare patients for bone-marrow transplant also damages their bones, leaving childhood cancer survivors who have received the transplants with low bone density, low muscle mass and high body fat over the long run.

But a Stanford team led by Judith Shizuru, MD, PhD, professor of medicine and of pediatrics, and Maria Grisatza Roncoronato, MD, professor of pediatrics and of medicine, is developing an antibody-based method of preparing patients for bone-marrow transplant that is intended to allow them to skip radiation. "They're the first to do a stem cell transplant that doesn't require radiation, and we have an opportunity to see if this incredibly new therapy prevents fractures in those patients," Leonard said.

Her team hopes their discoveries will translate into better ways to keep kids' bones strong for decades to come. "Bone fractures are painful, and the young patients we're studying already face other medical problems," said Sheldon. "Ultimately, we want to strengthen their bones so they can be happier and more active in childhood and throughout their adult lives as well."

COURTESY OF THE LEONARD LAB
professor of psychiatry and behavioral sciences. Researchers had previously hypothesized that parents might drive the link between attitude and achievement — perhaps children with more positive attitudes toward math because they found it more rewarding or motivating. “Instead, we saw that if you have more positive attitudes toward math, it results in enhanced memory and more efficient engagement of the brain’s problem-solving capacities,” Chen said.

The researchers administered standard questionnaires to 2,400 children ages 7 to 10, including tests of demographics, IQ, reading ability and working-memory capacity. The children’s level of math achievement was measured with tests of their knowledge of arithmetic facts and ability to solve math word problems. Parents or guardians answered surveys about the children’s behavioral and emotional characteristics, as well as their anxiety about math and general anxiety. Children also answered a survey that assessed their attitude toward math, including questions about interest in math and self-perceived math abilities.

Forty-seven children from the group also performed a mental-arithmetic test while performing arithmetical problems. Tests were conducted outside the MRI scanner to discern which problem-solving strategies they used. An independent scanner to discern which problem-solving strategies they used. An independent.

In the trial, patients were evaluated at treatment centers between six and 16 hours after incurring strokes originating in either of two large arteries in the brain. The middle cerebral artery or the internal carotid artery, which together account for about 25 percent of all strokes and the majority of severely disabling strokes.

“Patient selection matters,” Albers said. “Only about half of the patients we screened with the brain-imaging software had enough salvageable brain tissue to enter the study. For the others, the procedure was not an option.”

The AHA has issued new acute-stroke treatment guidelines that reflect what the study found.

Key to the study’s findings is a growing understanding of the anatomy of the brain tissue at different rates. Albers said. It’s not so much the amount of time elapsed since a stroke began as the amount of remaining at-risk but salvageable brain tissue that determines who will benefit from stroke therapy, he said.

The investigators used the brain-imaging software to rapidly evaluate blood-flow data generated from incoming patients. Albers developed the software about a decade ago with study co-author Roland Bammer, PhD, an associate professor of radiology at Stanford and now a professor at the University of Melbourne in Australia, and software engineer Matus Straka, PhD, who was then at the University of California, Davis.

Thrombectomy

Thrombectomy involves guiding a catheter stent through the circulatory system to the site of an acute stroke patient’s brain clot, where the stent then encases the clot and physically extracts it. The procedure is currently recommended only for patients who arrive within six hours of stroke onset. “As many as 35 to 40 percent of all strokes occur during sleep, so the short window of time severely limits the number of stroke patients getting this procedure. Another treatment, intravenous injection of a clot-dissolving substance, has an even tighter AHA-recommended window — just five to six hours — and isn’t very effective for treating large clots.

In the trial, patients were evaluated at treatment centers between six and 16 hours after incurring strokes originating in either of two large arteries in the brain. “I really cannot overstate the size of this effect.”

“Characteristics that determine who will benefit from stroke therapy are based on a combination of the size of the stroke and the amount of remaining brain tissue. We’ve shown in this study that different individuals’ strokes spread through the brain tissue to enter the study. For the others, the procedure was not an option.”

The seniors were randomized into two groups: One set of patients was then a senior scientist at Stanford.

Dr. Walter Koroshetz, MD, director of the National Institute of Neurological Disorders and Stroke, said in an NIH news release, “I really cannot overstate the size of this effect.”

Results of the trial were published online Jan. 24 in the New England Journal of Medicine. (See related story below.)

Walter Koroshetz, MD, director of the National Institute of Neurological Disorders and Stroke, said in an NIH news release, “I really cannot overstate the size of this effect.”

The findings may provide a new avenue for improving academic performance and learning in children who are at risk for mental health difficulties, Menon said, noting that this idea still needs to be tested through active interventions.

“By focusing specifically on skill-learning in individual academic domains, but our new study suggests that looking at children’s beliefs about a subject and their overall self-perceived abilities might provide another inroad to maximizing learning,” Menon said. The findings also offer a potential explanation for how a particularly passionate teacher can nurture students’ interests and learning capacities for a subject, he said. Inspirational teachers may be instinctively sharing their own interest, as well as instilling students in the belief that they can be good at the subject, building a positive attitude even if the student did not have it before.

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Charles K.F. Chan, PhD, was appointed assistant professor of surgery, effective Nov. 1. His group is investigating how stem cell niches change during tissue regeneration and aging and in diseases such as cancer.

Howard Chang, MD, PhD, professor of dermatology and the Virginia and D.K. Ludwig Professor of Cancer Genomics, received the 2018 National Academy of Sciences Award in Molecular Biology. The $25,000 award honors a young scientist who has made a recent notable discovery. He was recognized for his “insightful discoveries of long noncoding RNAs and technologies unveiling the noncoding genome.”

Jonathan Chen, MD, PhD, was appointed assistant professor of medicine, effective Nov. 1. His research focuses on mining clinical data sources to inform medical decision-making.

Michael Cherry, PhD, professor of genetics, has been awarded a $12.2 million grant as part of the National Institutes of Health Data Commons Pilot Phase. The four-year pilot project will explore how to make digital information available on collaborative platforms. With other investigators, he is responsible for the Alliance of Genome Resources data set, which will serve as a test case for the pilot project.

Ronald Dalman, MD, the Walter Clifford Chidester and Elsa Rooney Chidester Professor of Surgery, was elected to a three-year term on the board of governors and Elsa Rooney Chidester Professor of Surgery, was elected to a three-year term on the board of governors. The award recognizes distinguished society members who have made outstanding contributions to the field of experimental hematology.

Weissman, who holds the Virginia and D.K. Ludwig Professorship for Clinical Innovation in Cancer Research, also received a 2017 National Cancer Institute Outstanding Investigator Award, which recognizes accomplished leaders in cancer research and provides up to $600,000 a year for seven years. He plans to use the award to investigate whether mutations accumulate in a central nervous system stem cell clone that becomes a brain cancer stem cell.

He was awarded the 2017 Karl Landsteiner Memorial Award and Lectureship by the American Association of Blood Banking. The honor recognizes a scientist who has an international reputation in transfusion medicine or cellular therapies. Weissman was recognized for his pioneering role identifying and isolating the first hematopoietic stem cells in mice and humans.

He was awarded the Helmholtz International Fellow Award from the Helmholtz Association. The prize includes 20,000 euros (about $24,000) and an invitation to conduct research at one of the Helmholtz Centres. The Helmholtz Association of German Research Centres, funded by the German government, conducts research related to challenges facing society in several fields, including health.

In addition, he received an honorary doctorate from the Faculty of Medicine at the University of Turku in Finland.